Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: B

Pharma, Drug Discovery, Toxicology & Medicine

Highlights

A Review on Medicinal Plants

Study and Toxicity Evaluation

Granules Prepared with Stevia

Respiratory Acidosis in patients

Discovering Thoughts, Inventing Future

VOLUME 18 ISSUE 1 VERSION 1.0

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 18 Issue 1 (Ver. 1.0)

Open Association of Research Society

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

Global Journals Inc.

*(A Delaware USA Incorporation with "Good Standing"; **Reg. Number: 0423089**)*

Sponsors: Open Association of Research Society
Open Scientific Standards

Publisher's Headquarters office

Global Journals® Headquarters
945th Concord Streets,
Framingham Massachusetts Pin: 01701,
United States of America
USA Toll Free: +001-888-839-7392
USA Toll Free Fax: +001-888-839-7392

Offset Typesetting

Global Journals Incorporated
2nd, Lansdowne, Lansdowne Rd., Croydon-Surrey,
Pin: CR9 2ER, United Kingdom

Packaging & Continental Dispatching

Global Journals Pvt Ltd
E-3130 Sudama Nagar, Near Gopur Square,
Indore, M.P., Pin:452009, India

Find a correspondence nodal officer near you

To find nodal officer of your country, please email us at *local@globaljournals.org*

eContacts

Press Inquiries: *press@globaljournals.org*
Investor Inquiries: *investors@globaljournals.org*
Technical Support: *technology@globaljournals.org*
Media & Releases: *media@globaljournals.org*

Pricing (Excluding Air Parcel Charges):

Yearly Subscription (Personal & Institutional)
250 USD (B/W) & 350 USD (Color)

Editorial Board

Global Journal of Medical Research

Dr. Han-Xiang Deng

MD., Ph.D
Associate Professor and Research Department
Division of Neuromuscular Medicine
Davee Department of Neurology and Clinical Neurosciences
Northwestern University Feinberg School of Medicine
Web: neurology.northwestern.edu/faculty/deng.html

Dr. Pina C. Sanelli

Associate Professor of Radiology
Associate Professor of Public Health
Weill Cornell Medical College
Associate Attending Radiologist
NewYork-Presbyterian Hospital
MRI, MRA, CT, and CTA
Neuroradiology and Diagnostic Radiology
M.D., State University of New York at Buffalo,
School of Medicine and Biomedical Sciences
Web: weillcornell.org/pinasanelli/

Dr. Roberto Sanchez

Associate Professor
Department of Structural and Chemical Biology
Mount Sinai School of Medicine
Ph.D., The Rockefeller University
Web: mountsinai.org/

Dr. Michael R. Rudnick

M.D., FACP
Associate Professor of Medicine
Chief, Renal Electrolyte and Hypertension Division (PMC)
Penn Medicine, University of Pennsylvania
Presbyterian Medical Center, Philadelphia
Nephrology and Internal Medicine
Certified by the American Board of Internal Medicine
Web: uphs.upenn.edu/

Dr. Feng Feng

Boston University
Microbiology
72 East Concord Street R702
Duke University
United States of America

Dr. Seung-Yup Ku

M.D., Ph.D., Seoul National University Medical College,
Seoul, Korea Department of Obstetrics and Gynecology
Seoul National University Hospital, Seoul, Korea

Dr. Hrushikesh Aphale

MDS- Orthodontics and Dentofacial Orthopedics.
Fellow- World Federation of Orthodontist, USA.

Santhosh Kumar

Reader, Department of Periodontology,
Manipal University, Manipal

Gaurav Singhal

Master of Tropical Veterinary Sciences, currently pursuing Ph.D in Medicine

Dr. Aarti Garg

Bachelor of Dental Surgery (B.D.S.) M.D.S. in Pedodontics and Preventive Dentistr Pursuing Phd in Dentistry

Sabreena Safuan

Ph.D (Pathology) MSc (Molecular Pathology and Toxicology) BSc (Biomedicine)

Getahun Asebe

Veterinary medicine, Infectious diseases, Veterinary Public health, Animal Science

Dr. Suraj Agarwal

Bachelor of dental Surgery Master of dental Surgery in Oromaxillofacial Radiology.
Diploma in Forensic Science & Oodntology

Osama Alali

PhD in Orthodontics, Department of Orthodontics, School of Dentistry, University of Damascus. Damascus, Syria. 2013 Masters Degree in Orthodontics.

Prabudh Goel

MCh (Pediatric Surgery, Gold Medalist), FISPU, FICS-IS

Raouf Hajji

MD, Specialty Assistant Professor in Internal Medicine

Surekha Damineni

Ph.D with Post Doctoral in Cancer Genetics

Arundhati Biswas

MBBS, MS (General Surgery), FCPS, MCh, DNB (Neurosurgery)

Rui Pedro Pereira de Almeida

Ph.D Student in Health Sciences program, MSc in Quality Management in Healthcare Facilities

Dr. Sunanda Sharma

B.V.Sc.& AH, M.V.Sc (Animal Reproduction, Obstetrics & gynaecology), Ph.D.(Animal Reproduction, Obstetrics & gynaecology)

Shahanawaz SD

Master of Physiotherapy in Neurology PhD- Pursuing in Neuro Physiotherapy Master of Physiotherapy in Hospital Management

Dr. Shabana Naz Shah

PhD. in Pharmaceutical Chemistry

Vaishnavi V.K Vedam

Master of dental surgery oral pathology

Tariq Aziz

PhD Biotechnology in Progress

Contents of the Issue

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Studies on Majoon Aarad Khurma and its Granules Prepared with Stevia, with Reference to the Standardization and Toxicity Evaluation

By Mateen Ahmad Khan, Yasmeen Ansari, Roohi Zaman & Izharul Hasan

AIUMC Muzaffarnagar

Abstract- There is a huge treasure of Compound drugs described in various pharmacopoeias that have developed as a result of painstaking and cumulative efforts of elite scholars of Unani medicine. However, there has always been scope for inclusion of new compound drugs whose safety and efficacy has been proved scientifically.

Majoon Aarad Khurma which is widely used as an effective aphrodisiac is prepared with sugar as base. It is contraindicated in diabetic patients who are suffering from sexual dysfunctions. Preparation of medicines which are sugar free should be innovated or designed to meet the demand of the diabetic patients. Therefore the present study is aimed to develop granules of Majoon Aarad Khurma with natural sweetening agent *Stevia rebaudiana*. Granules are more convenient and comfortable in usage and dispensing. Granules uphold the same principles and maintain the same characteristics as traditional dosage forms, granules are safe, light, efficacious, stable and quality controlled.

Keywords: aphrodisiac, pharmacopoeias, diabetes, sexual dysfunction, granules, stevia rebaudiana, ccrum, sweetening agent.

GJMR-B Classification: NLMC Code: QV 4

STUDIESONMAJOONAARADKHURMAANDITSGRANULESPREPAREDWITHSTEVIAWITHREFERENCETOTHESTANDARDIZATIONANDTOXICITYEVALUATION

Strictly as per the compliance and regulations of:

Studies on Majoon Aarad Khurma and its Granules Prepared with Stevia, with Reference to the Standardization and Toxicity Evaluation

Mateen Ahmad Khan [α], Yasmeen Ansari [σ], Roohi Zaman [ρ] & Izharul Hasan [ω]

Abstract- There is a huge treasure of Compound drugs described in various pharmacopoeias that have developed as a result of painstaking and cumulative efforts of elite scholars of Unani medicine. However, there has always been scope for inclusion of new compound drugs whose safety and efficacy has been proved scientifically.

Majoon Aarad Khurma which is widely used as an effective aphrodisiac is prepared with sugar as base. It is contraindicated in diabetic patients who are suffering from sexual dysfunctions. Preparation of medicines which are sugar free should be innovated or designed to meet the demand of the diabetic patients. Therefore the present study is aimed to develop granules of Majoon Aarad Khurma with natural sweetening agent *Stevia rebaudiana*. Granules are more convenient and comfortable in usage and dispensing. Granules uphold the same principles and maintain the same characteristics as traditional dosage forms, granules are safe, light, efficacious, stable and quality controlled.

In present study an important Unani formulation i.e. Majoon Aarad Khurma has been modified into granules using *Stevia rebaudiana* as a sweetener and the safety and toxicity of the granules of Majoon Aarad Khurma has also been evaluated. Majoon Aarad Khurma and Granules of Majoon Aarad Khurma were prepared and subjected to Physico-Chemical evaluation with reference to the standards mentioned in Physicochemical Standards of Unani formulations by CCRUM.

Keywords: aphrodisiac, pharmacopoeias, diabetes, sexual dysfunction, granules, stevia rebaudiana, ccrum, sweetening agent.

I. Introduction

According to the Unani system of medicine, the health is a state of body in which there is equilibrium in humors and functions of the body. To maintain the correct humoral balance there is a power of self preservation called "Quwwate Mudabbirahe Badan" (Immunity of body) in the body.

Therefore the aim of the Unani physician is to find out the cause of the underlying disruption of humors, so that it can be corrected and disease can be cured. The temperament of the person is identified and diet/medicine/other recommendations are made that are most suitable for achieving and maintaining health of the particular person.

Sexual function is an important component of quality of life and subjective well being of humans. Human sexuality is a multidimensional phenomenon having biological, psychological, behavioral, clinical, moral and cultural aspects. It has been integral part of all cultures since time immemorial. But no single dimension of sexuality is universally dominant. Every person has sexual feelings, attitude and believes, but everyone's experience is unique because it proceeds through an intentionally personal prospective. The cardinal phases in sexual act in male are desire, erection, penetration and orgasm. The phases of sexual act in females are quite different from male. Usually in medicine and also in cultural aspects, sexuality has been mainly concerned with male sexual desire which increase in proportion to the level of secretion of the sex hormones. Sexual response is triggered by both psychological and physical stimuli. Sexual problems are widespread and adversely effects mood, well being, and inter-personal functioning.

Unani medicine treats sexual debility in its own way and proposes different methods of treatment Ilaj bil Ghiza (Ditotherapy), Ilaj bil Dawa (Pharmacotherapy) and Ilaj bit Tadbeer (Regimental therapy). Therapeutic use of the drugs is based on certain principles. The sexual problems are taken up in individualized way taking into account the entire personality of the patient [1]. Unani medicine has holistic approach towards diagnosis and treatment of sexual dysfunction that is not just confined to inability to perform the sex rather includes loss of libido, erectile dysfunction, ejaculatory insufficiency, an orgasmic state, excessive nocturnal emissions and even infertility in males, which may be due to Zoofe Bah (sexual dysfunction) or Nuqse Mani (seminal defects). It also distinguishes between sexual inadequacy and seminal inadequacy [2-4].

In present study an important Unani compound formulation Majoon Aarad Khurma has been modified into granular form using natural sweetening agent *Stevia rebaudiana* which has sweetening property as well as hypoglycemic activity, the granules of Majoon Aarad Khurma become palatable and will not cause any harm to diabetic patients who are suffering from sexual

Author α: Associate professor, Dept. of Ilmul Saidla, AIUMC Muzaffarnagar. e-mail: saurabh1468@gmail.com
Author σ: Lecturer, Dept. of Ilmul Qabalat-wa-Amraz-e-Niswan, AIUMC Muzaffarnagar.
Author ρ: Professor, Dept. of Ilmul Saidla, NIUM Bangalore.
Author ω: Consultant Unani, AWC, President Estate, Rashtrpati Bhavan, New Delhi.

dysfunction. This study also includes evaluation of physicochemical standards of Majoon Aarad Khurma and granules of Majoon Aarad Khurma and their safety and toxicity study.

II. Material and Methods

According to the protocol of the study "Studies on Majoon Aarad Khurma and its Granules prepared with Stevia, with reference to the Standardization and Toxicity Evaluation" Majoon Aarad Khurma and Granules of Majoon Aarad Khurma was prepared in the laboratory of Dept. of Ilmul Saidla, NIUM.

III. Preparation of Majoon Aarad Khurma

All the required ingredients of Majoon Aarad Khurma and Granules of Majoone Aarad Khurma were procured from the raw drug dealers under the supervision of the Guide, and all the raw drugs were identified and authenticated by the expert Dept. of Ilmul Advia, NIUM Bangalore, (Karnataka).

The Majoon Aarad Khurma was prepared as per the formulation mentioned in the National Formulary of Unani Medicine, Part-1, Govt. of India. The composition of Majoone Aarad Khurma is as given below:

Table 1: Ingredients of Majoon Aarad Khurma

Sl. No.	UNANI NAME	BOTANICAL NAME	PART USED	QUANTITY
1	Khurma	*Phoenix dactylifera*	Fruit	200gm
2	Samagh arbi	*Acacia arabica*	Gum	200gm
3	Singhara khushk	*Trapa bispinosa*	Fruit	200gm
4	Satawar	*Asparagus rasemosus*	Root	50gm
5	Jaiphal	*Myristica fragrans*	Nutmeg	1.25gm
6	Javitri	*Myristica fragrans*	Mace	1.25gm
7	Qaranfal	*Myrtus caryophyllus*	Flower Buds	2.5gm
8	Maghaze Badam	*Prunus amygdalus*	Fruit	25gm
9	Maghaze Chilghoza	*Pinus gerardiana*	Fruit	25gm
10	Maghaze Fundaq	*Corylus avellana*	Fruit	25gm
11	Maghaze Pambadana	*Gossypium herbaceum*	Fruit	5gm
12	Qand safaid	Sugar	Sugarcane	1kg

The dried raw drugs from 2-7 mentioned in table were powdered in mixer and sieved in (sieve number 80), raw drugs from 8-11 were powdered separately and sieved in (sieve number 40), and dates were separately dried in a hot air oven at 100°C for 4 hours then powdered and passed through (sieve number 60). Qiwam was prepared according to method mentioned in Formulary with 1 kilo sugar and 600 ml water; the dried drugs were mixed one by one in the Qiwam and stirred slowly. Finally all the Maghaziyat (Kernels) 8-11 were mixed gradually in the Qiwam. And stored in a container at room temperature for further study [5].

IV. Preparation of Granules of Majoon Aarad Khurma

The granule of Majoon Aarad Khurma was prepared as per the formulation mentioned in the National Formulary of Unani Medicine, Part-1, Govt. of India, the composition of granules of Majoon Aarad Khurma is as given below:

Table 2: Ingredients of granules of Majoon Aarad Khurma

Sl. No.	UNANI NAME	BOTANICAL NAME	PART USED	QUANTITY
1	Khurma	*Phoenix dactylifera*	Fruit	200gm
2	Kamagh arbi	*Acacia arabica*	Gum	200gm
3	Singhara khushk	*Trapa bispinosa*	Fruit	200gm
4	Satawar	*Asparagus rasemosus*	Root	50gm
5	Jaiphal	*Myristica fragrans*	Nutmeg	1.25gm
6	Javitri	*Myristica fragrans*	Mace	1.25gm
7	Qaranfal	*Myrtus caryophyllus*	Fruit	2.5gm
8	Maghaze Badam	*Prunus amygdalus*	Fruit	25gm
9	Maghaze Chilghoza	*Pinus gerardiana*	Fruit	25gm
10	Maghaze Fundaq	*Corylus avellana*	Fruit	25gm
11	Maghaze Pambadana	*Gossypium herbaceum*	Fruit	5gm
12	Stevia plant powder	*Stevia rebaudeana*	leaves	3.50gm

All the dried ingredients were powdered and sieved in (sieve number 80). All the Maghaziyat (kernels) were powdered separately and sieved in (sieve number 40), and dates were separately dried in a hot air oven at 100 °C for 4 hours and then powdered and passed through sieve number 60. *Stevia* plant extract was prepared with 120 ml water at low temperature for 15 minutes, and sieved through muslin cloth, the total quantity of this extract obtained was 80 ml. All the dried drugs were mixed one by one in Stevia extract, and subjected into the granulator (sieve number 20) for formation of granules and then stored in container at room temperature for further study [5].

V. Acute Toxicity Study

a) Experimental Animal

Swiss mice of both sexes, weighing 25-35 gm were used. The animals were procured from the, Sri Raghvendra Enterprises, Vijayanagar, Bangalore, Karnataka (India).

Prior to the experiment the animals were allowed to acclimatized for at least one week. They were maintained under standard laboratory conditions throughout the experimental period and were provided with standard diet and water *ad libitum* unless stated otherwise. They were housed in clean polypropylene cages at room temperature 25±2°C, humidity at 45-55% with 12 hours light: 12 hours dark cycle. The animal care procedures and experimental protocol were in according with the guidelines of CPCSEA.

b) Extractive Values [6]

For the determination of extractive values in non-successive of GMAK was carried out in Soxhlet apparatus, with hydro-alcoholic solvents i.e. 50% distilled water and 50% ethanol (1:1) ratio.

c) Methodology for Acute Toxicity Study [7, 8 - 15]

Acute toxicity test was performed according to the World Health Organization (WHO) guideline (WHO 2000) and the Organization of Economic Co-operation and Development (OECD) guideline for testing of chemicals 420 (OECD 2001). Swiss mice of either sex weighing 25-35 gram were randomly assigned to four groups (I, II, III, & IV,) of 7 mice each. Mice were fasted overnight (12 hrs) with free access to water prior to administration of single doses (0.398, 5.73, 9.73, & 16.69 g/kg b.wt.). The extract dissolved in distilled water and administered orally once a day. After the administration of the test drug all the animals were kept in polypropylene cages singly and were observed for Gross behaviour and mortality at 0 min, 30 min, 60 min, 120 min, 240 min and 24 hrs. The Gross behavioural changes such as piloerection, grooming, trembling, wriggling, diarrhoea, breathing difficulty, constant changing position, immobility, asthenia, anorexia, ataxia, urination and syncope were monitored continuously for any above abnormal changes.

VI. Physico-Chemical Evaluation

The Physico-Chemical studies were carried out on Majoon Aarad Khurma and Granules of Majoon Aarad Khurma in the laboratory of Dept of Ilmul Saidla, NIUM, Bangalore. Majoon Aarad Khurma and Granules of Majoon Aarad Khurma were prepared and subjected to Physico-Chemical evaluation under the following parameters:

(1) Organoleptic properties such as the appearance, colour, smell, and taste (2) Alcohol soluble matter and Water soluble matter (3) Successive extractive values (4) PH value (5) Bulk density and Tapped density (6) Ash value (7) Volatile oil (8) Saponification value (9) Iodine value (10) Acid value (11) Estimation of total Alkaloids (12) Resin (13) Reducing and non-Reducing sugars (14) Crude fibers (15) Thin layer chromatography (TLC) was also conducted for identification of compounds.

VII. Results and Observation

Both the test drugs sample Majoon Aarad Khurma and granules of Majoon Aarad Khurma were evaluated for physico-chemical parameters as recommended and almost all the values of both the test drugs were found within the standard limits.

Table 3: Physico-Chemical comparative data of MAK and GMAK

Sl. No	Physico Chemical Properties	MAK	GMAK
1.	Organoleptic Properties Apearance Odour Smell Taste	 Semi Solid Brownish Pleasant Sweet	 Granules Brownish Pleasant Sweet
2.	Alcohol Soluble Matter	65.5%	24.6%
3.	Water Soluble Matter	46.5%	36.6%
4.	Successive Extractives Petroleum Ether Chloroform Ethyl Alcohol Aqueous	 2.4% 0.4% 41.7% 35%	 4.2% 0.6% 19.13% 37.2

5.	PH Value 1% 10%	 4.90 4.32	 5.82 5.27
6.	Ash Value Total Ash Acid Insoluble Ash Water Soluble Ash	 0.66% 0.66% 1.33%	 2.5% 0.66% 1.16%
7.	Bulk Density Tapped Density Carr's Index Hausner Ratio		0.6gm/ml 0.68gm/ml 12% 1.13
8.	Volatile oils Traces	0.1%	0.1%
9.	Saponification Value	680.13	77.07
10.	Iodine Value	4.29	1.14
11.	Acid Value	4.21	2.80
12.	Alkaloids Total	0.13%	3.52%
13.	Resin Estimation	15.1%	37.2%
14.	Determination of Resin	15.2%	37.2%
15.	Reducing sugar	9.2%	15.6%
16.	Non-Reducing sugar	32.11%	24.2%
17.	Crude Fibers	1.13%	2.62%
18.	TLC Rf Values	0.27 0.31 0.50	0.31 0.36 0.50 0.68 0.75

VIII. Chemical Evaluation

a) Thin Layer Chromatography: [16- 29]

Thin layer chromatography was carried out on T.L.C. pre coated aluminium plates, silica gel 60 F 254 (layer thickness 0.25 mm) for ethanolic extract of both the test drug samples MAK and GMAK in various mobile phases, later sprayed by different spraying reagents to visualise the spots. The R_F values of the spots were calculated for both the drugs by the following formula.

$$R_f \text{ Value} = \frac{Distance\ \ travelled\ \ by\ Spot}{Distance\ \ travelled\ \ by\ Solvent}$$

Table 4: TLC of Majoon Aarad Khurma and granules of Majoon Aarad Khurma

Extract	Solvent System	No. of Spots	R_f Value	Colours
MAK Ethanol	Toluene: Ethyl acetate (7:3, with 2 drop Sulphuric acid)	3	0.27	Green
			0.31	Yellow
			0.50	Pink
GMAK Ethanol	Toluene: Ethyl acetate(7:3, with 2 drop Sulphuric acid)	5	0.31	Green
			0.36	Brown
			0.50	Light Pink
			0.68	Pink
			0.75	Yellow

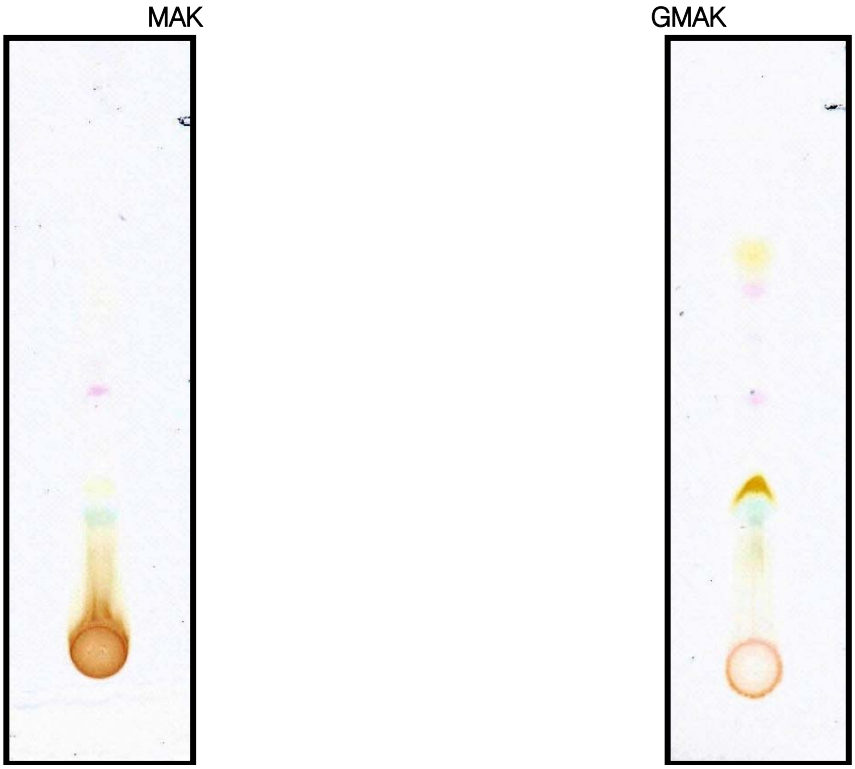


Fig. 1: TLC plates high lighting the spots in MAK and GMAK

b) Acute Toxicity Study

The acute toxicity study was done on Swiss mice of either sex using Hydro-Alcoholic extract of granules of Majoon Aarad Khurma orally, no behavioural changes and mortality was found during 24 hours observation period.

IX. Discussion

Majoon Aarad Khurma is one such popular drug which is widely used as an effective aphrodisiac, which is prepared with sugar as base but as we know that the intake of sugar is not advisable in diabetic patients because the presence of sugar in large amount in blood may develop the complications of diabetes more rapidly so any preparation having sugar as a base or content may create such risk. So even after gaining such popularity as an aphrodisiac, Majoon Aarad Khurma cannot be given to diabetic patients who are suffering from erectile dysfunction. Hence sugar free an alternate formulation should be innovated or designed to meet the demand of the diabetic patients.

X. Conclusion

The Physicochemical standards for scientific evaluation of Majoon Aarad Khurma and granules of Majoon Aarad Khurma were estimated and the standards were evaluated as recommended by CCRUM.

Based on the finding it is concluded that

- Granules possessed the same principles and maintained same characteristics as traditional dosage form Majoon Aarad Khurma.
- The granules of Majoon Aarad Khurma were found to be more stable, convenient and comfortable in usage and dispensing, and also safe, light, efficacious, cost effective and quality controlled.
- Stevia a natural sweetening agent which was used as base for granules was evaluated for its toxicity in animal models and no toxicity was found, hence Stevia can be used as safe and efficacious sweetening agent in preparation of granules as well as in other Unani formulations.

References Références Referencias

1. McCary JL and Mc Carry SP. *Aphrodisiac and Anaphrodisiacs in Mccary's Human Sexuality*. 4th ed. 1974: 227-33.
2. Basheer A. *Risalae Quwwate Bah*. Kanpur: Munshi Naval Kishore; 1886. pnm.
3. Khan MN. A scientific study of some Unani drugs used for improving the male sexual function. Aligarh- *Thesis* submitted to Dept. of Ilmul Advia, A.K.T.C, A.M.U; 1993:
4. Moben FAM. *Qanoone mubasharat*. Delhi: Jamia Barqi Press; 1934: pnm.

5. Said HM. *Hamdard Pharmacopoeia of Eastern Medicine.* New Delhi: Sri Sat Guru Publications; 1997: 9-10, 259, 353.
6. Mohammad TH. *Evaluation of lithotriptic activity of Tukhme Karafs (seeds of Apium graveolens Linn) in experimental animals*, Dept. of Ilmul Advia, NIUM, Bangalore, 2010.
7. *Acute and sub-chronic oral toxicity studies of an aqueous stem bark extract of Pterocarpus soyauxii Taub (Papilionaceae) in rodents*; Journal of Ethnopharmacology 133 (2011) 329–335.
8. Irshad S. Temperature standardization and comparative toxicity study of Kushta Sammul Far prepared by different methods, *Thesis*. Dept. of Ilmul Advia, NIUM, Bangalore, 2009.
9. Ibn Baitar. *Aljame al Mufradat al Advia wa al Aghzia*. Vol.1st. Urdu translation by CCRUM New Delhi: Dept of AYUSH, Ministry of H & FW. Govt. of India; 1999: 136, 349, 437.
10. Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone London, England, 1988. Evaluation of tapioca sago starch as a binder in tablet formulation. *IJPI's Journal of Pharmacognosy and Herbal Formulations* 2010; 1(1).
11. Afaq SH, Tajuddin and Siddiqui MMH. *Standardization of herbal drugs.* Aligarh: Publication AMU Aligarh: 100.
12. Sutharsingh R, Kavimani S, Jayakar B, Uvarani M, Thangathirupathi A. Quantitave phytochemical estimation and antioxidant studies on aerial parts of *Naravelia zeylanica* dc. *International Journal of Pharmaceutical Studies and Research* 2011 April June; II (II): 52-56.
13. Harborne JB. *Phytochemical methods*, London: Chapman and Hall, Ltd. 1973; 49-188.
14. Vogel. *Elementary practice organic chemistry, qualitative organic analysis.* Part 3. Great Britain: Longman Group Limited; 1970: 743.
15. Hertzel C, Gerstein. *Evidence-Based Diabetes Care*; BC Decker Inc Hamilton, London: 2001: 531.
16. Siddique AB. et al., *Chemical composition of essential oil by different extraction methods and fatty acid analysis of the leaves of Stevia Rebaudiana Bertoni.* Arabian Journal of Chemistry (2012), doi:10.1016/j.arabjc.2012.01.004.
17. Luo, H. et al., Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine. A systematic review of randomized clinical trials. J. Ethnopharmacol. (2012), doi: 10.1016/j.jep.2012.01.031.
18. Fan T.P. et al., Future development of global regulations of Chinese herbal products. J. Ethnopharmacol. (2012), doi:10.1016/j.jep.2012.02.029.
19. Niharika Sahoo et al., *Herbal drugs: Standards and regulation. Department of Biotechnology, West Bengal, India*. Fitoterapia 2010; 81: 462–471.
20. Jenkins GL, Knevel AM and Digangi FE. *Quantitative Pharmaceutical Chemistry*. 6th ed. New Delhi: CBS Publishers; 2008: 243-253, 379.
21. Goodman and Gilman's. *The Pharmacological Basis of Therapeutics*. 10th ed. U.S.A: Mc Graw-Hill, Medical publishing Division; 2001: 1687.
22. http://wiki.answers.com/Q/What_is_a_non-reducing_sugar [cited Dec. 2011: 15/122011].
23. Shamsi. Standardization and Pharmacological Evaluation of two Nervine Unani Formulations, *Thesis.* Aligarh: Dept. of Ilmul Advia, AMU; 2008: 85.
24. Kinsey et al. 1948 cited by Masters WH, Johnson VE, Kolodny RC. *Masters and Johnson on Sex and human loving.* Mumbai: Jaico publishing house; 2002: 572.
25. Kabiruddin HM. *Al-Akseer*. Vol. 2nd, New Delhi: Ajaz publication House, 2003: 1254-1284.
26. Siddique MSH, Ashraf SM and Siddiqui MMH. *Impotence: Unani concepts and its management,* The Journal of Research and Education in Indian Medicine. 1992: 14-17.
27. Sahib Singh R. *The Effect of Testosterone on the Cavernous Tissue and Erectile function;* World J. Ural 1997; 15, 21.
28. www.diabetes.niddk.nih.gov/dm/pubs/complications.
29. Rance J, Phillips C, Davies S, et al. *How much of a priority is treating erectile dysfunction:* a study of patients' perceptions. *Diabetic Med* 2003; 20: 205-9.

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Review on Huntington's Disease

By Dharmender Jaglan
Keshav College of Pharmacy

Abstract- Neurodegenerative diseases exemplified by Alzheimer's and Huntington disease are characterized by the progressive neuropsychiatric dysfunction and loss of specific neuronal subtypes.

Huntington's disease (HD) is a devastating neurodegenerative disorder that occurs in patients with a mutation in the huntingtin or IT15 gene. Patients are plagued by early cognitive signs, motor deficits, and psychiatric disturbances. Symptoms are attributed to cell death in the striatum and disruption of cortical–striatal. Mechanisms of cell death are unclear, but processes involving mitochondrial abnormalities, excitotoxicity, and abnormal protein degradation have been implicated. Many factors likely contribute to neuron death and dysfunction and this has made it difficult to systematically address the pathology in HD. Pharmaceutical therapies are commonly used in patients to treat disease symptoms. These have limited benefit and do not address the inexorable disease progression. Several neuroprotective therapies are being evaluated in animal models of HD as well as in clinical trials. Similarly, cell replacement strategies such as fetal transplantation have been used in the clinic with minimal success, making future cell replacement strategies such as stem cell therapy uncertain. This review describes the disease pathology and neurochemistry of HD and addresses many of the past and emerging therapeutic strategies.

Keywords: *huntington's disease; symptoms; therapies; cell death.*

GJMR-B Classification: *NLMC Code: WL 359.5*

Strictly as per the compliance and regulations of:

A Review on Huntington's Disease

Dharmender Jaglan

Abstract- Neurodegenerative diseases exemplified by Alzheimer's and Huntington disease are characterized by the progressive neuropsychiatric dysfunction and loss of specific neuronal subtypes.

Huntington's disease (HD) is a devastating neurodegenerative disorder that occurs in patients with a mutation in the huntingtin or IT15 gene. Patients are plagued by early cognitive signs, motor deficits, and psychiatric disturbances. Symptoms are attributed to cell death in the striatum and disruption of cortical–striatal. Mechanisms of cell death are unclear, but processes involving mitochondrial abnormalities, excitotoxicity, and abnormal protein degradation have been implicated. Many factors likely contribute to neuron death and dysfunction and this has made it difficult to systematically address the pathology in HD. Pharmaceutical therapies are commonly used in patients to treat disease symptoms. These have limited benefit and do not address the inexorable disease progression. Several neuroprotective therapies are being evaluated in animal models of HD as well as in clinical trials. Similarly, cell replacement strategies such as fetal transplantation have been used in the clinic with minimal success, making future cell replacement strategies such as stem cell therapy uncertain. This review describes the disease pathology and neurochemistry of HD and addresses many of the past and emerging therapeutic strategies.

Keywords: huntington's disease; symptoms; therapies; cell death.

I. Introduction

Huntington's disease is a genetic, progressive, neurodegenerative disorder characterized by the gradual development of involuntary muscle movements affecting the hands, feet, face, and trunk and progressive deterioration of cognitive processes and memory (dementia). Neurologic movement abnormalities may include uncontrolled, irregular, rapid, jerky movements (chorea) and athetosis, a condition characterized by relatively slow, writhing involuntary movements (Novak MJ, *et al.,* Huntington's disease. BMJ.2010). Dementia is typically associated with progressive disorientation and confusion, personality disintegration, impairment of memory control, restlessness and

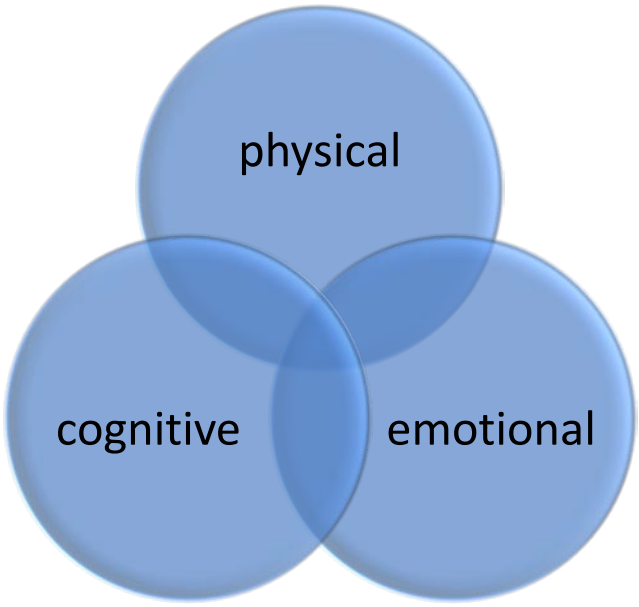


Fig. 1: Difficult Behaviors In Huntington's Disease

II. Epidemiology

Huntington's disease is currently found in many different countries and ethnic groups around the world. There are varying rates of prevalence in different racial groups 2. HD has a worldwide prevalence of five to 288 eight per 100,000 people with no gender preponderance. The highest frequencies of HD are found in Europe and countries of European origin. The lowest frequencies are documented in Africa, China, Japan, and Finland.

Author: Keshav College of Pharmacy, Salwan (Haryana).
e-mail: dharmenderjaglan@gmail.com

a) Symptoms

The symptoms of HD vary widely from person to person, even within the same family. For some, involuntary movements may be prominent even in the early stages. For others, these may be less evident and emotional and behavioral symptoms may be more obvious. The following are common features of HD:

b) Motor Symptoms

Motor Symptoms Physical symptoms may initially consist of "nervous" activity, fidgeting, twitching, or excessive restlessness. Handwriting may change and facial grimaces may appear. Day-to-day skills involving coordination and concentration, such as driving, become more difficult. These initial symptoms will gradually develop into more marked involuntary movements of the head, trunk and limbs – which often lead to problems in walking and balance. Speech and swallowing can become impaired. Movements generally tend to increase during voluntary effort, stress or excitement, and decrease during rest and sleep.

c) Cognitive Symptoms/ Intellectual Symptoms

Slight intellectual changes are often the first signs of cognitive disturbance. Short-term memory loss may occur while long-term memory generally stays intact. Disorganisation as a result of difficulties with planning, initiating, and organising thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information (Rothlind J *et al.;* 1993).

d) Psychiatric//Behavioral Symptoms

Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hyper sexuality (uncommon), psychosis (uncommon), Some people can experience depression for a period of months or even years before it is recognized to be an early symptom of Huntington's. Behavioral changes may include aggressive outbursts, impulsiveness, mood swings, and social withdrawal. Often, existing personality traits will be exacerbated by HD, e.g., a person who had a tendency to be irritable. Schizophrenia and other serious psychiatric problems are uncommon in HD but do occur.

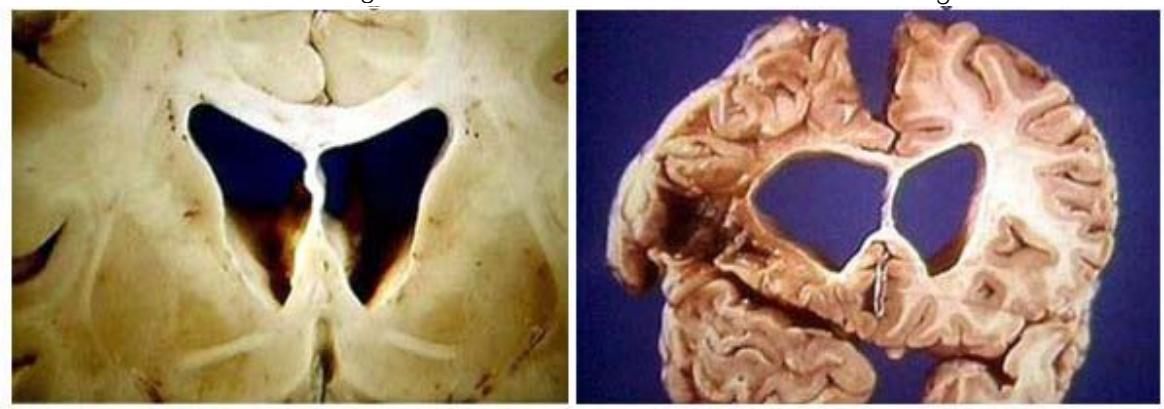
e) Metabolic

Weight loss, sleep disturbance

III. Neuropathology of Huntington's Disease

The specific symptoms and progression of HD can be related to its pathology, which is characterized by the loss of specific neuronal populations in many brain regions. Motor dysfunction in HD results from the disruption of basal ganglia-thalamocortical pathways regulating movement control (Garrett EA, *et al*., 1990 and Graybiel AM. 1990). The primary site of neuronal loss and atrophy in HD brain is in the caudate- putamen (Browne SE, 1999) Vulnerability in HD. The striatum is composed of a variety of medium to large neurons that differ in their size and dendritic profile as well as neurochemical content and output. Severe loss of medium sized striatal neurons was seen in the HD brain. They have large dendritic tree and use GABA as their neurotransmitter (Hassel B, *et al*., 1995).

Normal Basal Ganglia VS. HD Basal Ganglia



The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region

a) Effect of HD on Basal Ganglia

As these neurons degenerate in HD, the neurochemical they contain, including glutamic acid decarboxylase (GAD), substance-P, enkephalin, calcineurin, calbindin, adenosine receptors and dopamine receptors, also decrease. Number of theories has been presented, to determine the exact events involved in the progression of cell deaths caused by HD. One theory proposes that neurons die in HD because of an over-accumulation of normal excitatory chemicals

involved in nerve impulses. Excitatory neurotransmitters (mainly glutamate) are normally present in the brain, but, if they are released in excessive amounts or if brain cells are weak, these excitatory chemicals can cause cell damage and become chemicals known as "excitotoxins." Studies show that when glutamate is injected into the basal ganglion region of brains of living rats, the rats exhibit symptoms of HD (Reddy HP, *et al*., 1999). This first theory had to be modified when high levels of glutamate were not found in the brains of all HD patients. The mitochondrial dysfunction plays a role in pathogenesis of HD. The mitochondria of striatal cells may be damaged with the onset of HD. Scientists today believe that the damaged mitochondria of people with HD make striatal cells unable to produce as much energy as they need, which then makes the cells more susceptible to normal levels of glutamate (Beal MF. 2000). Another theory to explain the death of nerve cells postulates that the cells actually kill themselves in response to chemical changes caused by HD. HD triggers the early death of neurons by accelerating a normal process called apoptosis (Gutekunst AC, *et al*., 2000). 3-Nitropropionic acid and malonate also induce apoptotic profiles and induce pro-apoptotic proteins (Hickey MA, *et al*., 2003). To sum up, the neurobiological effects of HD appear to be the result of a number of different changes that ultimately go out of control. Many studies have shown that neurodegeneration is not confined to the basal ganglia but also occurs widely in cortical and other sub cortical regions.

b) Pathogenesis of Huntington's Disease and Huntingtin Protein

Huntington's disease is caused by the abnormal expansion of a CAG-trinucleotide repeat in the N-terminal exon 1 of the huntingtin gene, which is located on the short arm of chromosome 4 (4p16.3) (The Huntington's Disease Collaborative Research Group. 1993; Brouillet, E. *et al.,* 1999; Brennan, W.A. *et al.,* 1985). In the translated protein, huntingtin, this repeat encodes an expanded polyglutamine repeat sequence. Asymptomatic individuals have the wild type huntingtin gene with 29 or fewer CAG repeats, while HD is caused by expansions of 36 or more repeats (Rubinsztein, D C, *et al.,* 2002; Rubinsztein, D.C. *et al.,* 1996). There is an inverse relationship between the genomic CAG repeat size of the mutant huntingtin gene and the age of onset of signs. The larger the number of CAG repeats, the earlier the age of disease onset. Most adult-onset cases have CAG repeat sizes ranging from 40-50, whereas expansions of more than 55 repeats frequently cause the juvenile form of the disease (Vonsattel, J.P. *et al.,* 1998). Since the discovery of the huntingtin gene, an explosion of research has led to many insights into the normal function of huntingtin and the molecular basis of the disease. The normal or wild type huntingtin protein is found mainly in the cellular cytoplasm. This cytoplasmic protein is ubiquitously and widely expressed in many different tissues but its expression is highest in neurons. Huntingtin protein has been found in vesicle membranes, the cytosol, the nucleus, mitochondria, and microtubules. It appears to be associated with clathrin through huntingtin-interacting protein (HIP-1) (DiFiglia, M. *et al.,* 1995; Panov, A.V. *et al.,* 2002; Trottier, Y. *et al.,* 1995). These intracellular locations suggest that huntingtin may act as a molecular scaffold regulating several cellular processes including clathrin-mediated endocytosis, vesicle transport, synaptic transmission, transcriptional events and mitochondrial function (Rubinsztein, D.C. 2002; Young, A.B. 2003; Harjes, P. et al., 2003; Metzler, M. et al., 2001; Waelter, S. et al., 2001; Sugars, K.L. 2003. Furthermore, huntingtin can protect neuronal cells from apoptotic stress and therefore may have a pro-survival role as well (Rigamonti, D. et al., 2000; Leavitt, B.R. *et al.,* 2001). The number of huntingtin interacting proteins identified up to now exceeds 25 (Li, S.H. *et al.,* 2004. Collectively, the role of huntingtin is complex and it appears to be involved in various cellular functions both in the cytoplasm and nucleus (reviewed in (Li, S.H. *et al.,* 2004). The precise function of normal huntingtin is not yet fully understood and how mutant huntingtin exerts harmful effects remains unclear (Young, A.B. 2003). Various hypotheses have been proposed. For example, the mutant huntingtin protein may be neurotoxic through transcriptional dysregulation or it may make neurons susceptible to excitotoxicity, associated with an increase in cytosolic calcium (Harjes, P. et al., 2003; Bossy-Wetzel, E. et al., 2004). Moreover, mutant huntingtin also dysregulates mitochondrial homeostasis early in the disease (Panov, A.V. *et al.,* (2002) that may cause the release of cytochrome c and the activation of caspases. These proteins are involved in apoptosis (Rangone, H. *et al.,* (2004). Evidence is accumulating of both a toxic effect of mutant huntingtin fragments and a depletion of wild type huntingtin as part of the pathogenesis in HD (Friedlander, R. 2003; Rigamonti, D. *et al.,* 2000; Chen, M. *et al*., 2000; Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Zuccato, C. *et al.,* 2001; Landles, C. *et al.,* 2004). Neurons of HD patients contain one copy of the wild type huntingtin allele and one copy of the mutant huntingtin allele. Possibly as part of normal proteolysis of huntingtin, a N-terminal fragment containing the expanded polyglutamine repeat is released. This expanded polyglutamine-containing fragment then undergoes a conformational change and this ultimately, through as yet unknown steps and structures, results in toxic protein aggregates *that* also recruit other proteins (Gutekunst, C.A. *et al.,* 2002; Ona, V. *et al.,* 1999; Wellington, C.L. *et al.,* 2000; Hackam, A.S. *et al.,* 1998; Li, S.H. *et al.,* 2000; Mende-Mueller, *et al.,* 2001). These huntingtin aggregates can be found in any part of a neuron, but primarily in the nucleus

(Harjes, P. *et al.,* 2003; Li, S.H. *et al.,* 2004). Huntingtin protein aggregates become ubiquinated, presumably because they are recognized as misfolded proteins that become targeted for proteasomal degradation. The process of toxic aggregate formation may thus be critical for the development of neuronal dysfunction and degeneration in HD (Gutekunst, C.A. *et al.,* 2002). However, a direct causative pathway from the huntingtin gene mutation to the neostriatal degeneration has not yet been established. For example, it is not clear whether the formation of cytoplasmic aggregates and nuclear inclusions, the presence of soluble aberrant mutant huntingtin fragments, or an intermediary structure is the crucial determinant of neuronal cell death and disease initiation and progression. Several other mechanisms that may contribute to neuronal dysfunction and cell death in HD, which are not directly related to mutant huntingtin, have been proposed to play a role in the disease process. These include impaired energy metabolism by mitochondrial dysfunction, glutamate-mediated excitotoxicity, oxidative stress, altered gene transcription abnormal protein interactions and inappropriate apoptosis (Landles, C. *et al.,* 2004; Ho, L.W. *et al.,* 2001). In neurons with compromised energy metabolism, the threshold for glutamate toxicity is reduced. This leads to activation of glutamate-mediated excitotoxicity, whereas induced oxidative stress increases the production of damaging and free oxygen and nitrogen radicals. Mitochondrial dysfunction also causes the release of cytochrome c and activates caspases, and thus, could be a central phenomenon in HD pathogenesis as it would explain the oxidative stress, excitotoxic processes and energy metabolism dysfunction observed in HD patients (Rangone, H. *et al.,* 2004). How cells die in HD is not clear and whether the dying cells have been dysfunctional for a considerable time before cell death is also unknown. The problem that investigators face is to distinguish primary from secondary events in elucidating the pathogenesis of HD. For now it is not clear whether mitochondrial dysfunction is a primary change or a consequence of the early neuropathological changes in HD (Rubinsztein, D.C. 2002; Landles, C. *et al.,* 2004; Bates, G.P. *et al.,* 2002; Bates, G.2003; Jones, L., 2002). The pathogenesis of HD could well be multifactorial as is the huntingtin protein, which may have many functions.

c) Apoptosis and Huntington's Disease

HD is caused by an abnormal expansion of a CAG-trinucleotide repeat in the huntingtin gene but the precise mechanism of the selective neurodegeneration in HD neostriatum remains unclear. It has been suggested that aberrant apoptosis is involved in the pathogenesis of Huntington's disease (HD) (Wellington, C.L. *et al.,* 1997; Petersén, Å. *et al.,* 1999). Initial studies demonstrated an increase in DNA degradation and (Thomas, L.B. *et al.,* 1995; Dragunow, M. *et al.,* 1995; Portera-Cailliau, C. *et al.,* 1995). In vitro studies have shown substantial evidence connecting apoptotic pathways and apoptosis with mutant huntingtin (Hickey, M. *et al.,* 2003). Although it is not known how mutant huntingtin promotes cell death, a self-amplification cascade of progressive caspase activation that leads to neuronal dysfunction and eventually cell death has been proposed (Goldberg, Y. *et al.,* 1996; Hickey, M. *et al.,* 2003). Huntingtin is proteolysed by caspase-1 and caspase-3 (Wellington, C.L. *et al.,* 2000; Goldberg, Y. *et al.,* 1996). In HD mouse models and in presymptomatic and early symptomatic stages of HD patients caspase-1 and caspase-3 gene expression is transcriptionally up-regulated (Chen, M. *et al.,* 2000). This leads to an increase of caspase-mediated cleavage of huntingtin and increases the generation of N-terminal huntingtin fragments that are prone to form toxic aggregates in neurons (Ona, V. *et al.,* 1999; Wellington, C.L. *et al.,* 2000; Goldberg, Y. *et al.,* 1996; Hackam, A.S. *et al.,* 1998), while depleting wild type huntingtin (Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Kiechle, T. *et al.,* 2002). It appears that some features of HD result from the depletion of huntingtin protein function, whereas recent data have shown that the consequent N-terminal toxic fragments themselves may exert toxic effects on the cell by transcriptional disrupting of other genes (Landles, C. *et al.,* 2004; Hickey, M. *et al.,* 2003; Nucifora, F.C., Jr. *et al.,* 2001). This evidence suggests that caspases are not only mediators of cell death but also of cell dysfunction, possibly more important for HD pathogenesis than for apoptotic cell death alone. Moreover, in human HD striatal brain tissue, activation of several pro- apoptotic proteins, such as Bax, caspases 1, 3, 8, and 9 and release of cytochrome c have been demonstrated (Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Kiechle, T. *et al.,* 2002; Vis, J.C. *et al.,* 2005). Despite this, morphological evidence of apoptotic neuronal death in human HD is scarce. Which pathways are involved in apoptosis remains unclear. In this thesis, we studied apoptotic cell death and the expression of apoptotic markers in animal models of HD and in human HD brains that may contribute to the slowly developing death of medium-sized spiny GABAergic projection neurons in the striatum.

IV. Neurochemistry of Hutington's Disease

Neurochemical alterations in HD have long attention from researchers. The pathological changes in HD are caused by neurochemical. Neurochemical alterations are the essential mediators of Huntington's disease pathogenesis which not only produce the characteristic clinical symptoms of HD but also accelerate the process of cell death (Browne SE, *et al*., 1999).

V. Genetics of HD

The disease gene for HD, huntingtin, was identified in 1993 and it encodes a large protein (348kDa) with a polyglutamine stretch named huntingtin (Htt) (Sawa A, *et al*., 2003 and The Huntington's Disease Collaborative Research Group: 1993). Genetic defect in HD is an expansion of an unstable CAG repeats encoding polyglutamines at the 5' end of a huntingtin [also termed "interesting transcript 15" (IT15)] gene on chromosome (Hickey MA, *et al*., 2003). The biological function of the huntingtin protein is still unknown; it is known that the alteration of this protein ultimately results in HD (Bao J, *et al*., 1996 and Reddy, 1999).

Estimates of the prevalence of HD range from 4.1-8.4 per 100,000 people. In the United States, it is estimated that 25000 individuals have HD with another 125,000 individuals at risk (Harper PS.1986). In India: A recent study on the distribution of C-A-G repeats in the normal population suggests a higher prevalence of HD in India closer to that seen in Western Europe. Based on the results, haplotype analysis suggested the presence of a founder mutation in a subset of families and provide evidences for multiple and geographically distinct origins for HD mutation in India. One of the studies conducted on 124 (94 male and 30 female) elderly patients (aged more than 60 years) in a teaching hospital in India reported that there were 2.4% cases of HD, Parkinson's disease in India (Jha S, *et al*., 2004).

VI. Neuropsychological and Neuropsychiatric Aspects of HD

HD, an inherited neurodegenerative disease, damages specific areas of the brain resulting in movement difficulties as well as cognitive and behavioral changes. The cognitive changes in HD have traditionally been referred to as dementia. People with HD have specific and characteristic cognitive difficulties, with other aspects of cognitive function remaining well preserved. Behavioral changes are a characteristic feature of HD and are often the most distressing aspect of the condition for individuals and families dealing with HD (Harper PS.1986). Behavioral changes associated with HD Psychomotor function - Early motor signs of HD typically include the gradual onset of clumsiness, balance trouble, tremor and brief random, fidgeting movements. The primary involuntary movement abnormality and often the earliest symptom, is chorea or choreoathetosis, continuous and irregular writhing and jerking movements (Van Raamsdonk JK, *et al*., 2005). Many HD patients develop a distinctive manner of walking (gait) that may be unsteady, disjoined, or lurching as disease progresses (Delval A, 2006 and Naarding et al., 2001). Frustration, Irritability, Aggression & Anxiety- People suffering from HD may remain even-tempered; others may lose the ability to control their emotions. Emotional volatility may evident in increased irritability or episodes of explosiveness (Van Raamsdonk *et al*., 2005). These individuals may become irritable, frustrated or aggressive if demands are not met. Anxiety, a behavioral symptom of HD, is characterized by nervousness, restlessness, fidgeting, shallow breathing, sweating, fear, and panic rapid heart rate (Klivenyi P, *et al*., 2006). For individuals with HD, continual life changes as HD progresses can be a source of anxiety. Depression is often dismissed as an understandable reaction being diagnosed with HD (Paulsen JS, *et al*., 2005). Altered Sexuality - A very common behavioral symptom of HD is altered sexuality. Possible cause is that the delicate balance of hormones in the brain is disrupted by the progression of HD causing changes in behaviors regulated by hormone levels. Most commonly, people with HD suffer from a decreased sex drive. Increased sex drive and inappropriate sexual behavior are less common alterations of sexuality resulting from HD (Cummings JL. 1995). Cognitive changes in HD, The term "cognitive" refers to tasks of the brain that involve knowing, thinking, remembering, organizing and judging. Cognitive changes in the HD may be due to the disruption of striatal –frontal circuits (Baudic S, *et al*., 2006) Memory and Visual spatial ability an individual suffering from the cognitive symptoms of HD may have memory difficulties. Several investigators have shown that memory recall is generally affected more than memory storage in HD (Baudic S, *et al*., 2006). It is important to note that the memory problems that can occur in people with HD are different from the memory difficulties that can occur in people with Alzheimer's disease (AD) (Lundervold AJ, *et al*., 1994). Most commonly, the individual suffering from cognitive symptoms of HD is aware of his or her visual spatial impairment. Reading difficulties may also be the result of visual spatial impairment; however, the inability to maintain attention may be a contributing factor as well (Anderson KE, *et al*., 2005).

VII. Management of HD

Huntington's disease is a devastating neurological disorder without effective treatment. There is an urgent need for developing effective therapies for HD.

VIII. Treatment of Chorea

Dopamine blocking or dopamine depleting medications Increase dopamine level plays a major role in the pathogenesis of HD. On the basis of these reports dopamine-depleting drug like Tetrabenzine was also used for the treatment of chorea in clinical trial (Hannan JA. 2004). But due to lot of side effects the FDA did not approve this drug. Glutamate antagonism Excitotoxicity is the major cause of death of neurons in the HD. Increase in glutamate release activate the NMDA

receptors and increase the level of Ca 2+ and cause neurotoxicity. The drugs, which block the NMDA receptors, may be useful to decrease the symptoms of HD (Verhagen ML, et al., 2002). GABAergic modulation GABA an inhibitory neurotransmitter is decreased in the HD brain and cerebrospinal fluid. Indeed the GABA mimetic drugs and GABA transminase inhibitors are also be used in the clinical trial for the treatment of HD (Bonelli MR, et al., 2004). Cannabinoids receptor agonists In the brain the cannabinoids and their receptors behave as neurotransmitters or neuromodulators in a variety of processes, such as the regulation of motor behaviour, cognition, learning, memory and antinociception. It is also reported that the cannabinoid receptors are destroyed in the basal ganglia (Becker LI, et al., 2003). Therefore the treatment with cannabinoids could be beneficial for HD. Antioxidants One component of excitoxicity in HD is oxidative stress and antioxidants may therefore have therapeutic utility. A novel antioxidant, BN-82451 improved motor ability and survival and ameliorated neurodegenration in R6/2 HD mice (The Huntington's Disease Collaborative Research Group: 1993 and Hannan JA. 2004).

a) Neurodegeneration and Huntington's Disease

Neurodegeneration diseases have been characterized by progressive dysfunction and death of cells that affect specific neural systems. Neuronal loss is associated with misfolding and aggregation of proteins leading to accumulation of abnormal extracellular and intracellular filamentous deposits in specific cells types, mainly neurons and glia, representing the features of many neurodegeneration disorder (Mattson, 2006). Common pathogenic mechanism which cause neurodegeneration disorders are:

1. Oxidative stress and formation of free radicals / reactive oxygen species (ROS).
2. Mitochondrial dysfunction.
3. Neuroinflammatory dysfunction / neuro-immune response.
4. Abnormal protein dynamics with protein misfolding, defective protein degradation and aggregation.

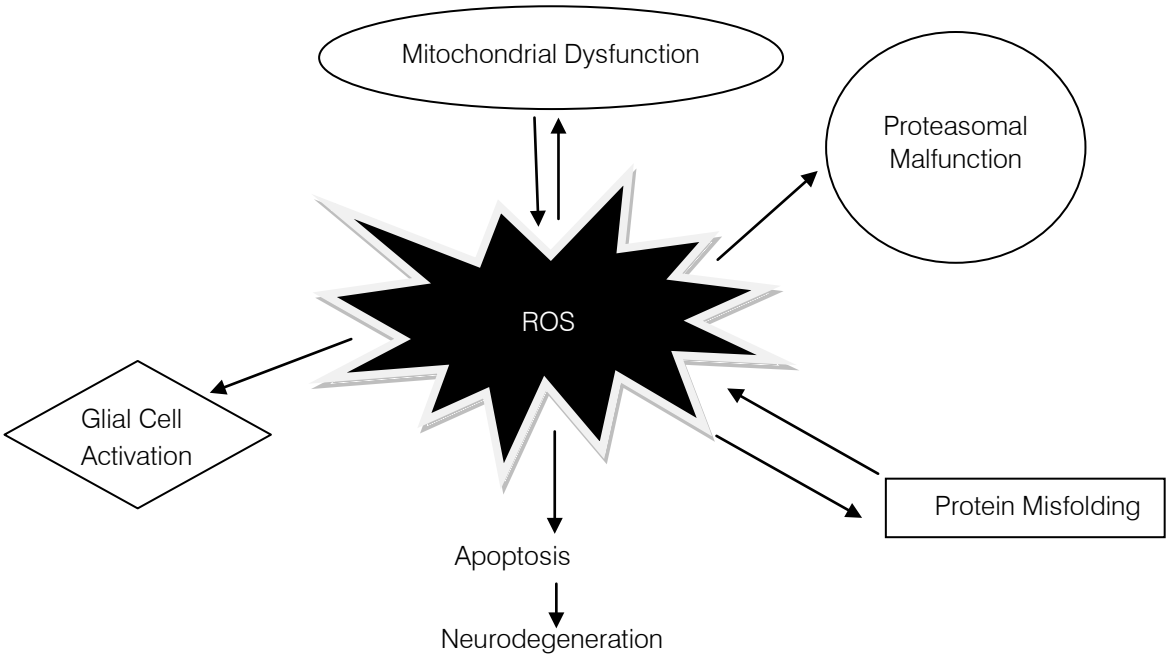


Fig. 2: Different mechanism leading to neurodegeneration

Dysfunction of mitochondrial energy metabolism leads to reduced ATP production, impaired calcium puffering, and generation of reactive oxygen species (ROS). Generation of reactive oxidants, including ROS is increased in damaged mitochondrial and in cells with compromised mitochondrial function.

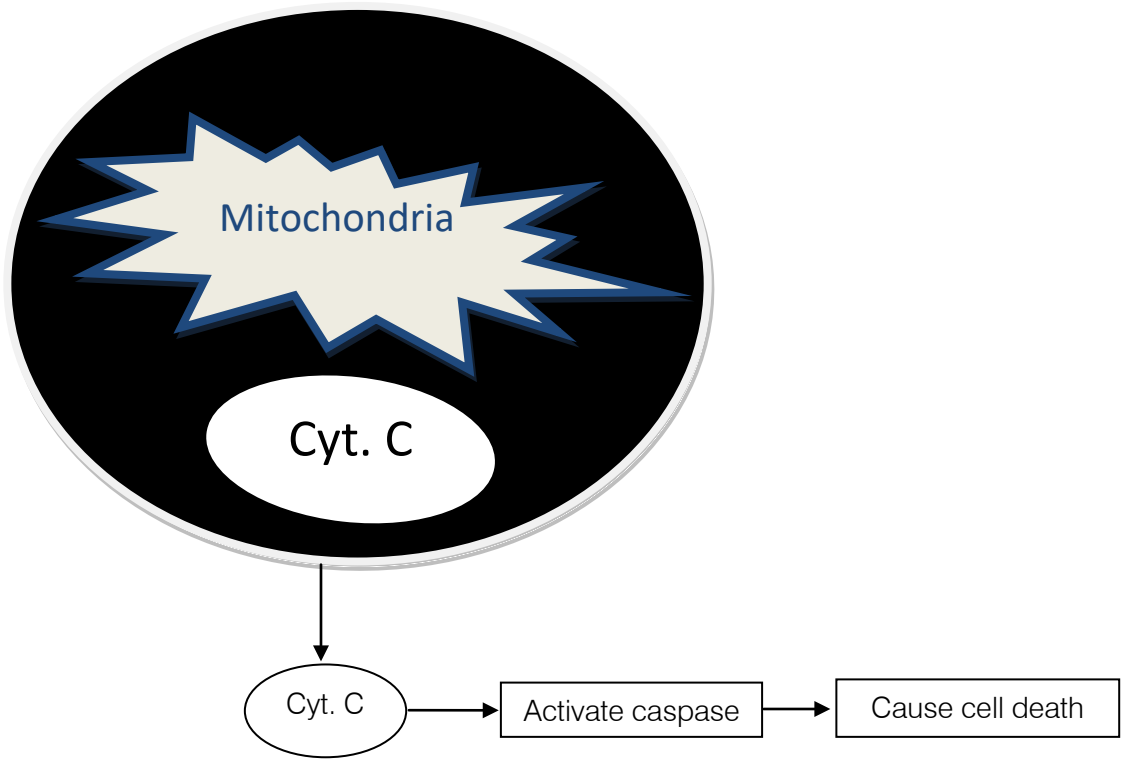


Fig. 3: Cascade leading to neuronal death related to mitochondria defects

Acute exposure of high levels of oxidant can induce the mitochondrial permeability transition (MPT), uncouple oxidative phosphorylation with catastrophic effect on mitochondrial energetics and contribute to cytotoxicity via necrosis or apoptosis through release of cytochrome c etc (Kwong JQ,2006).

On the other hand proteasomal inhibition reduced mitochondrial complex 1 and 11 activities, increased mitochondrial reactive oxygen species (ROS) production and increased the presence of damage production in autophogosomes (Sullivan P,2004).

IX. Inflammation and Huntington's Disease

Inflammation in the brain and the rest of the central nervous system (CNS) is a key factor in neurodegenerative diseases. Inflammation plays a significant role in the progression of HD. The previous Studies of the HD brain indicate that long-term inflammation plays a significant role in the progression of HD. It is suggested that excitotoxic amino acids such as glutamate induce a direct activation and proliferation of cells involved in inflammation. Since glutamate activity is also implicated in the progression of HD, it is possible that the glutamate molecules in the HD brain induce an inflammatory response (Arzberger T, et al., 1997). One of the first steps in excitotoxic neuronal damage involves the hyperstimulation of N-methyl-D-aspartate (NMDA) receptors leading to a massive calcium influx that activates, among other processes, the calcium dependent phospholipase A2 (PLA2). Further, PLA2 cleaves membrane phospholipids to yield arachidonic acid (AA), a free fatty acid, which is converted by cyclooxygenases (COX) into prostaglandins (PGs). The inflammatory response results in the activation of various types of cells and the production of different molecules that can lead to cell death (Kukreja RC, et al., 1986).

An example of cells activated by the inflammatory response is the microglia (a type of immune cell), which have been found to be highly activated in the HD brain. Research has shown that there is an activated microglia is found along the vicinity of nerve cells that contain neuronal inclusions (NIs) – accumulation of the huntingtin protein. This finding suggests that the huntingtin protein accumulation influences the activation of reactive microglia. Nerve cell injury due to excitotoxins such as glutamate also induces long-term microglial activation in the brain (Arzberger T, et al., 1997 and Kukreja RC, et al., 1986).

Neuro-inflammation is mediated by soluble pro-inflammatory molecules such as cytokines, prostaglandins and nitric oxide (N.O) (Silvestroni *et al.,* 2009). While some mediators such as IL, TNF-α were increased in striatum and some mediators such as IL-6, IL-8 were also upregulated in cortex .Microglia, the resident immune cells of the CNS, play a critical role in inflammation-mediated neurodegeneration. An example of cells activated by the inflammatory response is the microglia, which has been found to be activated in the HD brain. Normally, microglia cells in their resting state vigilantly monitor the health of neurons. In brain damage

or infection, microglia cells become activated and may secrete a variety of inflammatory mediators and neurotoxic factors. Activated microglia cells trigger and maintain an inflammatory response, deluging neurons with a whole host of inflammatory mediators that may ultimately lead to neuronal cell death. Neurodegenerative CNS diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and age-related macular degeneration (ARMD), are all associated with chronic neuro-inflammation and elevated levels of several cytokines. Microglial activation and chronic inflammation thereafter is the starting point for elevated levels of a wide array of potentially neurotoxic molecules including pro-inflammatory cytokines, proteinases, and reactive oxygen species (ROS) (Boje, K *et al.,* 1992, Chao et al., 1995, Chao *et al.,* 1992, Jeohn *et al.,* 1998 and Xie *et al.,* 2002). Suppression of microglial production of neurotoxic mediators will result in neuroprotection (Glass *et al.,* 2010 and Ransohoff, R *et al.,* 2009).

a) Oxidative Stress in HD

HD is an autosomal dominantly inherited progressive neurodegenerative disorder, affecting people in middle age. HD is characterized by the progressive development of involuntary choreiform movements, cognitive impairment, neuropsychiatric symptoms, and premature death. The etiology of HD is unknown, but increasing evidence suggests important roles of altered gene transcription, mitochondrial dysfunction, excitotoxicity, and oxidative stress (Gardian, G, *et al.,* 2004). Oxidative stress has been implicated in the neural dysfunction and death observed un neurodegenerative conditions such as Alzheimer's disease (AD) (Butterfield *et al.,* 2002a; Buterfield *et al.,* 2002b), Parkinson's disease (PD) (Blum *et al.,* 1997), as well as HD (Browne et al., 1999; Goswami *et al.,* 2006; Chen *et al.,* 2007). Cells normally produce free radicals as by products of aerobic respiration and other metabolic processes (Grunewald *et al.,* 1999). These free radicals include reactive oxygen species (ROS). ROS are highly reactive oxidant and can have deleterious effects on cellular lipids, proteins, and DNA. Cells normally have enzymes and coenzymes that act as antioxidant. These are able to neutralize ROS and prevent them from causing damage (Heales *et al.,* 2002). ROS include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), nitric acid (NO) and hydroxyl radicals (OH) (Keller *et al.,* 2001). The primary site of the production of these free radicals is the mitochondrion (Fleury *et al.,* 2002). Superoxide is produced within the mitochondrion at complexes 1, 11, 111 and 1V of the electron transport chain. A single electron is transferred from the electron transport chain at these sites to molecular oxygen. The reaction of superoxide with H^+ catalyzed by superoxide dismutase (SOD) produces H_2O_2 (Keller et al., 2001; Klein et al., 2003). H2O2 reacts with the transition metals cu+ or Fe2+ via the Fenton reaction to produce the hydroxyl radical. NO is produced by nitric oxide synthase (NOS), which catalyzes the conversion of arginine to citrulline and NO. NO can react with superoxide to produce the Peroxynitrite free radicals (Deckel *et al.,* 2001).

Oxidative stress is defined as the imbalance between biochemical processes which are responsible for the production of reactive oxygen species (ROS) and those responsible for removal of ROS *(Browne S et al., 1997).* Oxidative Stress is the common denominator of the disease. HD is widely distributed in both neurons and extraneuronal tissues. Oxidative Stress plays an important role in HD pathogenesis. In Huntington's disease, the damage caused by oxidative stress includes lipid peroxidation, protein oxidation and DNA oxidation. 8-hydroxydeoxyguanaise (8-OHdn), an oxidized DNA marker which increased in the caudate of the HD patients *(Browne S et al., 1997).* The increased level of 8-OHdn in mitochondrial DNA of the parietal cortex was found in late stage of HD (Polidori M, *et al.,* 1999). Several studies have documented increased oxidative damage to DNA outside the brain of Huntington's disease patients by demonstrating increased 8- OHdn in HD peripheral blood (Chen C, *et al.,* 2007 *and* Hersch S *et al.,* 2006). Oxidative stress caused by N-terminal fragments of mutant htt which can be suppressed by over-expression of heatshock proteins in a HD cellular model.Oxidative stress could promote htt aggregation and mutant htt induced cell death by impairing proteosomal function. Oxidative damage has been associated with neuronal loss in HD (Goswami A *et al.,* 2006). These data indicate a role for oxidative stress in mediating HD and this may be alleviated by antioxidant therapy.

X. Development of Novel Therapeutics for HD

HD is a progressive disorder with fatal outcome. At present there are no effective treatments. Since the identification of the HD gene in 1993, great advancement in the understanding of the molecular biology and pathophysiology of the disorder has been occurred. The advances have suggested a new therapeutics strategy aimed at slowing disease progression or forestalling the onset of this devastating neurodegenerative disease. The treatment option available for HD are symptomatic which focus on neurological and psychiatric symptoms and aim to improve quality of life (Boneli and Hoffman, 2007). Agents that inhibit mutant huntingtin aggregation and Transglutaminase inhibitors. The huntingtin aggregates and inclusions play a major role in the pathogenesis of HD. Inhibit mutant huntingtin from aggregation would provide a way to prevent the progression of the disease

(Aiken CT, *et al.,* 2004). Transglutaminase (TGase) can use huntingtin as a substrate to cross-link huntingtin molecules. TGase activity was found to have increased in HD postmortem brains (Karpuj MV, et al., 2002). Cystamine is an inhibitor of TGase and showed a small but significant neuroprotective effect with improvement of motor function, survival and loss of bodyweight. Protease inhibitors Recent findings showed that huntington could be cleaved by proteases, including caspases, calpain, and aspartyl protease. Caspase and calpain-mediated partial cleavage of mutant huntingtin promotes huntingtin aggregation and cellular toxicity, inhibitors of huntingtin partial cleavage might have therapeutic values. Caspase inhibitors, z-VAD-fmk and z-DEVD- fmk, can prevent cleavage of huntingtin by caspases and reduce cytotoxicity caused by expanded polyglutamine tract (Chen M, et al., 2000). Caspase inhibitor minocycline was able to inhibit huntingtin aggregation, retard disease progress and prolong the lifespan of HD mice. Protease inhibitors could reduce N-htt fragments and in turn, prevent or delay disease progression (Wang X, et al., 2003). Histone deacetylase (HDAC) inhibitors Inhibitors of histone deacetylase (HDAC) can increase gene transcription and have been examined as a potential therapy in both HD Drosophila and transgenic R6/2 HD mice. Suberoylanilide hydroxamic acid (SAHA), a selective HDAC inhibitor, reduced neurodegeneration in HD Drosophila (Steffan JS, et al., 2001).

a) Other Neuroprotective Approaches Gene Therapy

Intracellular antibodies (intrabodies) and RNA interference (RNAi) are two potential methods that could be used for gene therapy of HD. Mitochondria dysfunction has been implicated in HD pathogenesis. Therefore, compounds enhancing energy metabolism have been evaluated for treatment of HD. Coenzyme Q10 and creatine are neuroprotective, putatively via enhancing cerebral energy metabolism (Browne SE, *et al.,* 1999; Qin ZH, *et al.,* 2004). Neural cell transplantation is also under development for the treatment of HD. Brain derived Neurotrophic factors: Brain derived neurotropic factor (BDNF) expression is reduced in the caudate and putamen of patients with HD. That enhanced expression of neurotropic factors may mitigate the effects of neurotoxins and thus be a potential therapeutic strategy was explored in animal and cell models (Bemelmans AP, et al., 1999 and Davis JD, et al., 2001).

References Références Referencias

1. Novak MJ, Tabrizi SJ. Huntington's disease. BMJ. 2010; 340: c3109. [PubMed: 20591965].
2. Sawa A, Tomoda T, Bae BI. Mechanisms of neuronal cell death in Huntington's disease. Cytogenet Genome Res. 2003; 100: 287-295.
3. Qin ZH, Zhen LGU. Huntingtin processing in pathogenesis of Huntington's disease. Acta Pharmacol Sin. 2004; 25: 1243-1249.
4. Jelliffe SE. A contribution to the history of Huntington's chorea: a preliminary report. Neurographs. 1908; 1: 116-1124.
5. Qrbeck AL. An early description of Huntington's chorea. Medical History. 1959; 3: 165-168.
6. Klein J. Woodie Guthrie. A life. London: Faber and Faber; 1981.
7. Harper PS. The epidemiology of Huntington's disease. Hum Genet. 1986; 89: 365-376.
8. Jha S, Patel R. Some observations on the spectrum of dementia. Neurol India 2004; 52:213-214. 10. Van Raamsdonk JM, Pearson J, Slow EJ, Hossain S.M, Leavitt BR, Hayden MR. Cognitive dysfunction precedes neuropathology and motor abnormalities in the YAC128 mouse model of Huntington's disease. J Neurosci. 2005; 25: 4169- 4180.
9. Delval A, Krystkowiak P, Blatt JL. Role of hypokinesia and bradykinesia in gait disturbances in Huntington's disease- A biomechanical study. J Neurol. 2006; 253: 73-80.
10. Naarding P, Kremer HPH, Zitman FG. Huntington's disease: a review of the literature on prevalence and treatment of neuropsychiatry phenomena. Eur Psychiatry. 2001; 16: 439-445.
11. Klivenyi P, Bende Z, Hartai Z. Behaviour changes in a transgenic model of Huntington's disease. Behav Brain Res 2006; 169: 137-141.
12. Paulsen JS, Nehl C, Hoth K.F. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci. 2005; 17: 496-502.
13. Cummings JL. Behavioral and psychiatric symptoms associated with Huntington's disease. Adv Neurol. 1995; 65: 179-186.
14. Baudic S, Maison P, Dolbeau G. Cognitive Impairment Related to Apathy in Early Huntington's disease. Dement Geriatr Cogn Disord. 2006; 21: 316-321.
15. Lundervold AJ, Reinvang I, Lundervold A. Characteristic patterns of verbal memory function in patients with Huntington's disease. Scand J Psychol. 1994; 35: 38-47.
16. Anderson KE, Marshall FJ. Behavioral symptoms associated with Huntington's disease. Adv Neurol. 2005; 96: 197-208.
17. Garrett EA, Crutcher MD. Functional architecture of basal ganglia circuits: Neuronal substrate of parallel processing. Trends in Neuroscience. 1990; 13: 266-271.
18. Graybiel AM. Neurotransmitters and neuro modulators in the basal ganglia. Trends in Neuroscience. 1990; 13: 244-254.
19. Browne SE, Ferrante RJ, Beal MF. Oxidative stress in Huntington's disease. Brain Pathol 1999; 9: 147-163.

20. Hassel B, Sonnewald U. Selective inhibition of the tricarboxylic acid cycle of GABAergic neurons with 3-nitropropionic acid in vivo. J Neurochem. 1995; 65: 1184-1191.
21. Reddy HP, Maya W, Danilo AT. Recent advances in understanding the pathogenesis of Huntington's disease. Trends in Neuroscience. 1999; 22: 248- 254.
22. Beal MF. Energetic in the pathogenesis of neurodegenerative disease. Trends in Neuroscience 2000; 23: 298-304.
23. Gutekunst AC, Francine N, Hersch MS. Recent advances in Huntington's disease. Current Opinion in Neurology. 2000; 13: 445-450.
24. Hickey MA, Chesselet MF. Apoptosis in Huntington's disease. Progress in Neuro-Psypharma & Bio Psych. 2003; 27: 255-265.
25. Faull RLM, Waldvogel HJ, Nicholson LFB, Synek BJL. The distribution of GABA A- benzodiazepine receptors in the basal ganglia in Huntington's disease and in quinolinic acid lesioned rats. Prog Brain Res. 1993; 99: 105-123.
26. Kleppner SR, Tobin AJ. GABA signalling: therapeutic targets for epilepsy, Parkinson's disease and Huntington's disease. Expert Opin Ther Targets. 2001; 5: 219-239.
27. Glass L, Dragunow M, Faull RLM. The pattern of neurodegenration in Huntington's disease: A comparative study of cannabinoid, dopamine, adenosine and GABA A receptors alterations in the human basal ganglia in Huntington's disease. Neuroscience. 2000; 97: 505-519.
28. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. Trends in Neuroscience. 1990; 13: 244-254.
29. Teunissen CE, Steinbusch HW, Angevaren M, Behavioural correlates of striatal glial fibrillary acidic protein in the 3-nitropropionic acid rat model: disturbed walking pattern and spatial orientation. Neuroscience. 2001; 105: 153-167.
30. Manyam BV, Giacobini E, Colliver JA. Cerebrospinal fluid acetylcholinesterase and choline measurements in Huntington's disease. J Neurol.1990; 237: 281-284.
31. Caboche J, Charvin D. Role of dopamine in Huntington's disease. Med Sci (Paris). 2006; 22: 115-127.
32. Starling AJ, Andre V.M, Cepeda C, de Lima M, Chandler SH, Levine MS. Alterations in N-methyl- D-aspartate receptor sensitivity and magnesium blockade occur early in development in the R6/2 mouse model of Huntington's disease. J Neurosci Res. 2005; 82: 377-386.
33. The Huntington's Disease Collaborative Research Group: Novel genes containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993l; 72: 971-983.
34. Bao J, Sharp AH, Waster MV. Expansion of polyglutamine repeat in huntingtin leads to abnormal protein interactions involving calmodulin. Proc Natl Acad Sci USA. 1996; 93: 5037-5047.
35. Arzberger T, Krampfl K, Leimgruber S, Weindl A. Changes of NMDA receptor subunit (NR1, NR2B) and glutamate transporter (GLT1) mRNA expression in Huntington's disease--an in situ hybridization study. J Neuropathol Exp Neurol. 1997; 56: 440-454.
36. Kukreja RC, Kontos HA, Hess ML, Ellis EF. PGH synthase and lipoxygenase generate superoxide in the presence of NADH or NADPH. Circ Res. 1986; 59: 612-619.
37. Leavitt RB, Wellington LC, Hayden RM. Recent insights into the molecular pathogenesis of Indian J. Pharm. Educ. Res. 41(4), Oct – Dec, 2007, 294.
38. Huntington's disease. Seminar in Neurology. 1999; 19: 385-395.
39. Hannan JA. Huntington's disease: which drugs might help patients? I Drugs. 2004; 7: 351-358.
40. Verhagen ML, Morris MJ, Farmer C, Gillespie M, Mosby K, Wuu J. Huntington's disease: a randomized, controlled trial using the NMDA-antagonist amantadine. Neurology. 2002; 59: 694– 699.
41. Bonelli MR, Gregor KW, Kapfhammer PH. Huntington's disease: present treatments and future therapeutic modalities. International Clinical Psycho-pharmacology. 2004; 19: 51-62.
42. Becker LI, Miguel RD, Ruzi JJF. The endocannabinoid system and Huntington's disease. Current Drug Targets-CNS & Neurological Disorders. 2003; 2: 335-347.
43. Aiken CT, Tobin AJ, Schweitzer ES. A cell-based screen for drugs to treat Huntington's disease. Neurobiol Dis. 2004; 16: 546-555.
44. Karpuj MV, Becher MW, Springer JE. Prolonged survival and decreased abnormal movements in transgenic model of Huntington disease with administration of the transglutaminase inhibitor cystamine. Nat Med. 2002; 8:143-149.
45. Chen M, Ona VO, Li M, Ferrante RJ, Fink KB, Zhu S. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med. 2000; 6: 797–801.
46. Wang X, Zhu S, Drozda M, Zhang W, Stavrovskaya IG, Cattaneo E. Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease. Proc Natl Acad Sci USA. 2003; 100: 10483–10487.
47. Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, Apostol BL0. Histone deacetylase inhibitors arrest polyglutamine dependent

neurodegeneration in Drosophila. Nature. 2001; 413: 739–743.
48. Bemelmans AP, Horellou P, Pradier L, Brunet I, Colin P, Mallet J. Brain-derived neurotrophic factor-mediated protection of striatal neurons in an excitotoxic rat model of Huntington's disease, as demonstrated by adenoviral gene transfer. Hum Gene Ther. 1999; 10: 2987–2997.
49. Davis JD, Filoteo JV, Maddox WT. A possible role of the striatum in linear and nonlinear category learning: evidence from patients with Huntington's disease. Behav Neurosci 2001; 123: 234-239.
50. Gardian, G., and Vecsei, L. (2004) Huntington's disease: patho- mechanism and therapeutic perspectives. J. Neural Transm. 111, 1485–1494.
51. Harjes, P. & Wanker, E.E. The hunt for huntingtin function: interaction partners tell many different stories. Trends Biochem Sci 28, 425-33 (2003).
52. Metzler, M. et al. HIP1 functions in clathrin-mediated endocytosis through binding to clathrin and adaptor protein 2. J Biol Chem 276, 39271-6 (2001).
53. Waelter, S. et al. The huntingtin interacting protein HIP1 is a clathrin and alpha- adaptin-binding protein involved in receptor-mediated endocytosis. Hum Mol Genet 10, 1807-17 (2001).
54. Sugars, K.L. & Rubinsztein, D.C. Transcriptional abnormalities in Huntington disease. Trends Genet 19, 233-8 (2003).
55. Rigamonti, D. et al. Wild-type huntingtin protects from apoptosis upstream of caspase- 3. J Neurosci 20, 3705-13 (2000).
56. Leavitt, B.R. et al. Wild-type huntingtin reduces the cellular toxicity of mutant huntingtin in vivo. Am J Hum Genet 68, 313-24 (2001).
57. Li, S.H. & Li, X.J. Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends Genet 20, 146-54 (2004).
58. Bossy-Wetzel, E., Schwarzenbacher, R. & Lipton, S.A. Molecular pathways to neurodegeneration. Nat Med 10 Suppl, S2-9 (2004).
59. Panov, A.V. et al. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5, 731-6 (2002).
60. Rangone, H., Humbert, S. & Saudou, F. Huntington's disease: how does huntingtin, an anti-apoptotic protein, become toxic? Pathol Biol (Paris) 52, 338-42 (2004).
61. Chen, M. et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med. 6, 797-801 (2000).
62. Ona, V. et al. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. Nature 399, 263-7 (1999).
63. Sanchez, I. et al. Caspase-8 is required for cell death induced by expanded polyglutamine repeats. Neuron 22, 623-33 (1999).
64. Zuccato, C. et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293, 493-8 (2001).
65. Landles, C. & Bates, G.P. Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO Rep 5, 958-63 (2004).
66. Wellington, C.L., Leavitt, B.R. & Hayden, M.R. Huntington disease: new insights on the role of huntingtin cleavage. J Neural Transm Suppl 58, 1-17 (2000).
67. Hackam, A.S. et al. The influence of huntingtin protein size on nuclear localization and cellular toxicity. J Cell Biol 141, 1097-105 (1998).
68. Li, S.H., Lam, S., Cheng, A.L. & Li, X.J. Intranuclear huntingtin increases the expression of caspase-1 and induces apoptosis. Hum Mol Genet 9, 2859-67 (2000).
69. Mende-Mueller, L.M., Toneff, T., Hwang, S.R., Chesselet, M.F. & Hook, V.Y. Tissue- specific proteolysis of Huntingtin (htt) in human brain: evidence of enhanced levels of N- and C-terminal htt fragments in Huntington's disease striatum. J Neurosci 21, 1830-7 (2001).
70. Ho, L.W. et al. The molecular biology of Huntington's disease. Psychol Med 31, 3-14 (2001).
71. Beal, M.F. Energetics in the pathogenesis of neurodegenerative diseases. Trends Neurosci 23, 298-304 (2000).
72. Bates, G.P. & Murphy, K.P. Huntington's disease. In Huntington's Disease (eds. Bates, G.P., Harper, P.S. & Jones, A.L.), Oxford University Press, Oxford, UK, 387-426 (2002).
73. Bates, G. Huntingtin aggregation and toxicity in Huntington's disease. Lancet 361, 1642- 4 (2003).
74. Jones, L. The cell biology of Huntington's disease. In Huntington's Disease (eds. Bates, G.P., Harper, P.S. & Jones, A.L.), Oxford Univeristy Press, Oxford, UK, 349-86 (2002).
75. Gutekunst, C.A., Norflus, F. & Hersch, S.M. The neuropathology of Huntington's disease. In Huntington's Disease (eds. Bates, G.P., Harper, P.S. & Jones, A.L.), Oxford University Press, Oxford, UK, 251-75 (2002).
76. Friedlander, R. Apoptosis and caspases in neurodegenerative diseases. N Engl J Med. 348, 1365-75 (2003).
77. Rigamonti, D. et al. Wild-type huntingtin protects from apoptosis upstream of caspase- 3. J Neurosci 20, 3705-13 (2000).
78. Li, S.H. & Li, X.J. Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends Genet 20, 146-54 (2004).
79. Landles, C. & Bates, G.P. Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO Rep 5, 958-63 (2004).

80. Rubinsztein, D.C. Lessons from animal models of Huntington's disease. Trends Genet 18, 202-9 (2002).
81. Gutekunst, C.A., Norflus, F. & Hersch, S.M. The neuropathology of Huntington's disease. In Huntington's Disease (eds. Bates, G.P., Harper, P.S. & Jones, A.L.), Oxford University Press, Oxford, UK, 251-75 (2002).
82. Harjes, P. & Wanker, E.E. The hunt for huntingtin function: interaction partners tell many different stories. Trends Biochem Sci 28, 425-33 (2003).
83. Li, S.H. & Li, X.J. Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends Genet 20, 146-54 (2004).
84. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72, 971-83 (1993).
85. Brouillet, E., Conde, F., Beal, M.F. & Hantraye, P. Replicating Huntington's disease phenotype in experimental animals. Prog Neurobiol 59, 427-68 (1999).
86. Brennan, W.A., Jr., Bird, E.D. & Aprille, J.R. Regional mitochondrial respiratory activity in Huntington's disease brain. J Neurochem 44, 1948-50 (1985).
87. Rubinsztein, D.C. et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. Am J Hum Genet 59, 16-22 (1996).
88. Rubinsztein, D.C. Lessons from animal models of Huntington's disease. Trends Genet 18, 202-9 (2002).
89. Vonsattel, J.P. & DiFiglia, M. Huntington disease. J Neuropathol Exp Neurol 57, 369-84 (1998).
90. DiFiglia, M. et al. Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron 14, 1075-81 (1995). 32. Panov, A.V. et al. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5, 731-6 (2002). 33. Trottier, Y. et al. Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. Nature 378, 403-6 (1995).
91. Wellington, C.L., Brinkman, R.R., O' Kusky, J.R. & Hayden, M. R. Toward understanding the molecular pathology of Huntington's disease. Brain Pathol 7, 979- 1002 (1997).
92. Petersén, Å., Mani, K. & Brundin, P. Recent advances on the pathogenesis of Huntington's disease. Exp Neurol 157, 1-18 (1999).
93. Dragunow, M. et al. In situ evidence for DNA fragmentation in Huntington's disease striatum and Alzheimer's disease temporal lobes. Neuroreport 6, 1053-7 (1995).
94. Portera-Cailliau, C., Hedreen, J.C., Price, D.L. & Koliatsos, V.E. Evidence for apoptotic cell death in Huntington disease and excitotoxic animal models. J Neurosci 15, 3775-87 (1995).
95. Thomas, L.B. et al. DNA end labeling (TUNEL) in Huntington's disease and other neuropathological conditions. Exp Neurol 133, 265-72 (1995).
96. Hickey, M. & Chesselet, M. Apoptosis in Huntington's disease. Prog Neuropsychopharmacol Biol Psychiatry. 27, 255-65 (2003).
97. Goldberg, Y. et al. Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. Nat Genet. 13, 442-9 (1996).
98. Chen, M. et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med. 6, 797-801 (2000).
99. Ona, V. et al. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. Nature 399, 263-7 (1999).
100. Sanchez, I. *et al.* Caspase-8 is required for cell death induced by expanded polyglutamine repeats. Neuron 22, 623-33 (1999).
101. Landles, C and Bates, G.P. Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO Rep 5, 958-63 (2004).
102. Wellington, C.L., Leavitt, B.R. & Hayden, M.R. Huntington disease: new insights on the role of huntingtin cleavage. J Neural Transm Suppl 58, 1-17 (2000).
103. Hickey, M. & Chesselet, M. Apoptosis in Huntington's disease. Prog Neuropsychopharmacol Biol Psychiatry. 27, 255-65 (2003).
104. Kiechle, T. et al. Cytochrome C and caspase-9 expression in Huntington's disease. Neuromolecular Med 1, 183-95 (2002).
105. Nucifora, F.C., Jr. et al. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291, 2423-8 (2001).
106. Vis, J.C. et al. Expression of apoptosis-related markers in human HD brains. Acta Neuropathol 109, 321-8 (2005).
107. Hackam, A.S. et al. The influence of huntingtin protein size on nuclear localization and cellular toxicity. J Cell Biol 141, 1097-105 (1998).

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Transdermal Buprenorphine Induced Respiratory Acidosis in a Post TKR Patient – A Rare Case

By Vishnu S, Sukesh Rao & A.V. Gurava Reddy
Sunshine Hospitals

Abstract- Post-operative pain management consists of a cocktail of drugs ranging from Nsaids, Opioids and Non-opioids. Transdermal Buprenorphine patch is commonly used in pain management of post-operative cases, musculoskeletal pain, cancerous and non-tumorous conditions. Buprenorphine is safely used because of its partial intrinsic activity and slow dissociation on Mu (μ) receptor causing prolonged analgesic effect with a ceiling for respiratory depression. Buprenorphine is commonly used in elderly patients and in patients with chronic renal failure. We report a probable case of buprenorphine patch induced respiratory depression and sedation leading to respiratory acidosis. Respiratory acidosis was managed symptomatically with oxygen therapy and removal of transdermal buprenorphine patch lead to the reversal of clinical condition. Awareness of this possible side effect of buprenorphine patch and unwarranted use should be avoided.

Keywords: *respiratory acidosis, buprenorphine, transdermal patch, respiratory depression.*

GJMR-B Classification: *NLMC Code: QV 55*

Strictly as per the compliance and regulations of:

Transdermal Buprenorphine Induced Respiratory Acidosis in a Post TKR Patient – A Rare Case

Vishnu S [α], Sukesh Rao [σ] & A.V. Gurava Reddy [ρ]

Abstract- **Post-operative pain management consists of a cocktail of drugs ranging from Nsaids, Opioids and Non-opioids. Transdermal Buprenorphine patch is commonly used in pain management of post-operative cases, musculoskeletal pain, cancerous and non-tumorous conditions. Buprenorphine is safely used because of its partial intrinsic activity and slow dissociation on Mu (μ) receptor causing prolonged analgesic effect with a ceiling for respiratory depression. Buprenorphine is commonly used in elderly patients and in patients with chronic renal failure. We report a probable case of buprenorphine patch induced respiratory depression and sedation leading to respiratory acidosis. Respiratory acidosis was managed symptomatically with oxygen therapy and removal of transdermal buprenorphine patch lead to the reversal of clinical condition. Awareness of this possible side effect of buprenorphine patch and unwarranted use should be avoided.**

Keywords: respiratory acidosis, buprenorphine, transdermal patch, respiratory depression.

I. Introduction

Opioid analgesics play a vital role in pain management. Post-operative analgesia involves a cocktail of drugs like NSAIDS, Anaesthetic blocks, Opioids and non- Opioids. Post-operative analgesia is also administered through various routes of oral, Intra-muscular, Intravenous, Epidural catheters, Anaesthetic blocks, infiltrations and latest one being the transdermal drug formulations [1]. Transdermal drug formulations provide a stable plasma drug concentration ensuring long lasting and adequate pain relief. These formulations are long acting, non-invasive, reduce morbidity and increased quality of life in patients [2].

Buprenorphine is a semi-synthetic derivative of the baine with a reactive alkaloid of morphine in it. It has a molecular weight of 467 and chemically an opioid because of the inclusion of a C-7 side chain containing a t-butyl group.

Pharmacological effects of buprenorphine are brought about by the binding of the molecule with μ (Mu), k (Kappa) and ϱ (Delta) receptors. It is a partial agonist at Mu receptor and antagonist at Kappa and Delta receptors. Analgesia is brought about through μ receptor action. It has a high affinity and low intrinsic activity towards Mu receptor. Buprenorphine demonstrates slow binding and delayed dissociation compared to morphine. The analgesic effects are sustained because of its activity on Mu receptor and doesn't cause abstinence syndrome on withdrawal of drug because of antagonistic action on Kappa and Delta receptor. Analgesic effects are also postulated because of agonistic activity on opioid receptor like receptor [ORL1] but has low affinity compared to other receptors [3]. Antagonist action on k and delta receptors shows less sedation, spinal analgesia and psycho-mimmetic effects than morphine or fentanyl [4].

Pharmacokinetic profile of buprenorphine is lipophilic and exhibits multiphasic clearance. It is highly protein bound mostly to alpha-globulin and beta-globulin fractions. Since most drugs bind to albumin there is no competition for binding proteins with less drug interactions. Oral Buprenorphine has low bio-availability of 15%. Buprenorphine has extensive first pass metabolism in GI mucosa and liver, it is conjugated with glucuronic acid and metabolised by CYP3A4 into buprenorphine and nor-buprenorphine. Nor-Buprenorphine which exerts a week analgesic action of minimal significance. End stage renal failure doesn't affect the excretion of drug [5].

Transdermal delivery systems which comes in various dosages and company brands. They have many advantages which primarily includes non-invasive administration and rate controlled delivery of drug[6]. They maintain a steady state of plasma concentration of drug. They have good patient tolerability and efficacy, commonly used in chronic pain states as cancer, non-cancerous conditions, chronic musculoskeletal pain conditions like osteoarthritis knee and low back ache. Clinical studies suggest that transdermal patch has increased the odds of more than 10 in functional improvement after buprenorphine patch in chronic musculoskeletal pain scenario. These transdermal systems have been designed to overcome the pharmacokinetic dis-advantages of oral and parenteral administration of drug which include poor gastrointestinal absorption, first pass metabolism and low bio-availability.

The increased analgesic potency of buprenorphine, lipophilic nature, low molecular weight and low addictive potential makes it an ideal drug of choice through transdermal route in management of

Author α σ ρ: Arthroplasty Division, Sunshine Hospitals, Secundrabad. e-mail: vishsnake@gmail.com

post-operative analgesia [7]. Transdermal buprenorphine doesn't have immunosuppressant effect at therapeutic analgesic doses unlike morphine and fentanyl.

Transdermal buprenorphine patches are advocated in the elderly population by the American Geriatric society for chronic pain conditions [8]. Society suggests buprenorphine patches as a first line management in chronic pain conditions followed by NSAIDS only when acute exacerbations are present. Buprenorphine can be used in renal failure and dose adjustment is not needed [9].

Transdermal patches use matrix technology which homogenously incorporates the drug in a solid matrix patch when applied to the skin and remained effective for a minimum duration of 72 hours to seven days [10].

Common side effects of transdermal buprenorphine are nausea, vomiting and less incidence of constipation compared to other opioids [11]. Respiratory depression is a potential complication of opioids which commonly includes Morphine, Methadone, hydromorphone, oxycodone and transdermal fentanyl [12]. Buprenorphine since having partial Mu receptor agonist activity, respiratory depression can occur. Respiratory depression due to buprenorphineis a rare complication which will have a slow onset and a longer duration compared to full Mu agonists like morphine, hence reversal with naloxone is difficult and also requires higher doses of naloxone for reversal. Buprenorphine has a ceiling effect or a bell shaped curve with regards to respiratory depression and analgesia at doses >1mg/kg and 0.1mg/kg. Ceiling effect on respiratory depression is not dependent doses used for analgesic action and recent literature suggests a linear dose response without any evidence of a ceiling effect in the therapeutic drug window. Ceiling effect provides safety profile for the drug which is not present with morphine or fentanyl. Reports of fatal respiratory depression have been rarely reported in literature mostly occurring in drug addicts [13].

In case of respiratory depression, management is to discontinue the drug delivery of buprenorphine, give oxygen mask, IV naloxone 2 mg stat over 90sec, commence naloxone 4mg/hour intravenously, continue monitoring till 90 min, monitor patient for next 24 hour and restart dose when the patient condition is satisfactory at a reduced dose[14].

Pharmaco - kinetically buprenorphine is metabolised in liver and its metabolism is not affected in patients with renal failure. The major metabolite being nor-buprenorphine which has low potency and low affinity of this metabolite to receptors and is less likely to cause toxicity in renal failure [15].

II. Case Report

We describe a case of a 78 year old female with a weight of 72 kg and 146 cm in height. The patient was posted for elective right total knee replacement. Pre-operative her blood parameters were Hb- 12.3 g/dl, urea-32 and creatinine–1.1. She was a known hypertensive on Tab. Calcigard 10 mg OD with ASA grade 2. Her spirometry report was in normal range.

She was operated for right total knee replacement and intra-operative period was uneventful. On post-operative day-1, she was shifted to general wing from surgical ICU and was put on buprenorphine patch of strength 10 μg/h for pain management near the incision site after dressing the wound. On POD-2, she became drowsy and was talking irrelevantly. Her saturation in room air was 84%. Her blood parameters showed sodium–138mmol/l and potassium-4.6mmol/l. Arterial Blood gas analysis from the femoral artery showed elevated PCo2 suggesting respiratory acidosis due to sedation effect and her respiratory inhalation wasn't strong. Patient was started on oxygen mask with 4L of oxygen and serial values of Arterial blood gas analysis were measured. The buprenorphine patch also was removed in view of suspicion of buprenorphine induced respiratory depression and respiratory acidosis.

The patient had a back ground of chronic renal failure with elevated creatinine with a value of 1.1-1.3 which could have added a metabolic component to the respiratory acidosis. Patient improved after the removal of patch. After two days, patient was mobilised and started on chest physiotherapy with deep breathing exercises. She was shifted to ward and discharged on day 5. The serial blood gas analysis values are showed in Table 1.

Table 1: Arterial Blood Gas Analysis Values

Parameter	Arterial Blood gas values at Admission(ICU)	Arterial Blood Gas Values at discharge(Ward)	Normal Values
PH	7.19	7.30	7.350-7.450
PCO2	55	40	32.0-48.0 mmHg
PO2	88	95	83.0-108 mmHg
HCO3-	20.9	24.3	21.0-28.0mmol/L
SPO2	84%	98%	98%

III. Discussion

Transdermal buprenorphine patches are commonly used in the post-operative period for pain management along with other analgesics [8]. In our patient, in view of her pre-operative elevated borderline creatinine values, she was only put on paracetamol injection through intra-venous route for pain. Her pain wasn't relieved and started on Buprenorphine patch. Buprenorphine being a semi-synthetic analogue of morphine have a partial mu receptor action causing analgesia with a ceiling effect for respiratory depression [9]. Transdermal buprenorphine patch causing respiratory depression in an adult is rarely reported in English literature.

We report a probable case of buprenorphine patch induced sedation and mild respiratory depression with a background of underlying chronic renal pathology. Old age with pain adding as a catalyst to the base line situation leading to respiratory acidosis and falling oxygen saturation values. The patient returned back to her physiological state after starting on oxygen, IV fluids, Input-output monitoring and removal of buprenorphine patch.

Awareness of such a pharmacological side effect of buprenorphine patch when used as a modality of pain management in elderly population. Buprenorphine patch induced respiratory depression has been reported in paediatric age but not in adults. We want to emphasize in our report, the careful use of morphine or buprenorphine patches in elderly population to avoid complications.

Consent: Obtained
Conflict of interest: None
Acknowledgements: None

References Références Referencias

1. Wilcock Andrew, Twycross Robert. Therapeutic Reviews. Journal of Pain and symptom management. 2013. 45(5): 939-949.
2. Raffa RB, Pergolizzi Jr JV. A modern analgesics pain 'pyramid'. J Clin Pharm Ther. 2014; 39: 4e6.
3. Davis MP. Twelve reasons for considering buprenorphine as frontline analgesic in the management of pain. J Support Oncol 2012; 10: 209-19.
4. Budd K. High dose buprenorphine for postoperative analgesia. Anaesthesia.1981; 36: 900–3.
5. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract 2010; 10: 428e50.
6. Berner B, John VA. 1994. Pharmacokinetic characterization of transdermal delivery systems. ClinPharmacokinet, 26: 121–34.
7. Likar R. Transdermal buprenorphine in the management of persistent pain–safety aspects. Therapeutics and Clinical Risk Management. 2006; 2(1): 115-125.
8. Budd K. Buprenorphine and the transdermal system: the ideal match in pain management. Int J ClinPractSuppl 2003; 133: 9e14. Discussion 23e4.
9. Likar R, Vadlau EM, Breschan C, Kager I, Korak-Leiter M, Ziervogel G. Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. Clin J Pain 2008; 24: 536e43.
10. Steiner DJ, Sitar S, Wen W, et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebocontrolled study. J Pain Symptom Manage. 2011; 42: 903e17.
11. Bach V, Kamp-Jensen M, Jensen N-H, et al. Buprenorphine and sustained release morphine – effect and side-effects in chronic use. The Pain Clinic.1991; 4: 87–93.
12. Kress GH. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. European Journal of Pain. 2009; 13: 219-230.
13. Budd K. Buprenorphine: a review. In: Evidence based medicine in practice. Newmarket, UK: Hayward Medical Communications. 2002, p 1–24.
14. Pergolizzi V Joseph, Scholten Willem, Smith J Kevin, Scott Leighton James, Wills C Jenna, Henningfeild Jack. The Unique role of transdermal buprenorphine in the global chronic pain epidemic. ActaAnaesthesiologica Taiwanica. 2015; 53: 71-76.
15. Desai SN, Badiger SV, Tokur SB. Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. Indian J Anaesth 2017; 61: 225-9.

This page is intentionally left blank

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 18 Issue 1 Version 1.0 Year 2018
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Review on Medicinal Plants used for Nausea and Vomiting in Persian Medicine

By Sharareh Darvishpor, Amirsaeed Hosseini, Ali Davoodi, Ebrahim Salehifar, Jafar Akbari & Mohammad Azadbakht
Mazandaran University of Medical Sciences

Abstract- Nausea and vomiting are common digestive symptoms of various illnesses, pregnancy, chemotherapy and motion sickness. They are very unpleasant and affect the quality of life. There are many drugs to control nausea and vomiting but in many cases they are uncontrollable, so helping to new drug discovery is necessary to control of these symptoms. This article showes the plants that used to control these syptoms in Persian medicine books such as: Canon of medicine, Al-Abnieah, Tohfeh, Ekhtiarat, Al-shamel and makhzanul-advieh. About 126 plants were identified to treatment of nausea and vomiting and in this paper 94 plants were presented. The most medicinal plants for the treatment were: *Citrus lemon, Berberis vulgaris, Malus domestica, Mentha piperita, Valeriana officinalis and Zingiber officinale*.

Keywords: plant, nausea; vomiting; traditional medicine; zingiber officinale.

GJMR-B Classification: NLMC Code: QV 55

Strictly as per the compliance and regulations of:

A Review on Medicinal Plants used for Nausea and Vomiting in Persian Medicine

Sharareh Darvishpor [α], Amirsaeed Hosseini [σ], Ali Davoodi [ρ], Ebrahim Salehifar [ω], Jafar Akbari [¥] & Mohammad Azadbakht [§]

Abstract- Nausea and vomiting are common digestive symptoms of various illnesses, pregnancy, chemotherapy and motion sickness. They are very unpleasant and affect the quality of life. There are many drugs to control nausea and vomiting but in many cases they are uncontrollable, so helping to new drug discovery is necessary to control of these symptoms. This article showes the plants that used to control these syptoms in Persian medicine books such as: Canon of medicine, Al-Abnieah, Tohfeh, Ekhtiarat, Al-shamel and makhzanul-advieh. About 126 plants were identified to treatment of nausea and vomiting and in this paper 94 plants were presented. The most medicinal plants for the treatment were: *Citrus lemon, Berberis vulgaris, Malus domestica, Mentha piperita, Valeriana officinalis and Zingiber officinale.*

Keywords: plant, nausea; vomiting; traditional medicine; zingiber officinale.

I. Introduction

Nausea and vomiting are common digestive problems that affect the quality of life. They also are common problems in patient with chronic disease conditions (40-70%) such as cancer. Nausea and vomiting can be disease or adverse effect of drugs. It can be due to various reasons such as: motion sickness, pregnancy, stomach irritation, chemotherapy, and post-operative factors [1-3].

Nausea is an unpleasant subjective sensation and a feeling close to vomiting. Vomiting includes two stages; retching stomach and exit of the material through the mouth [4, 5].

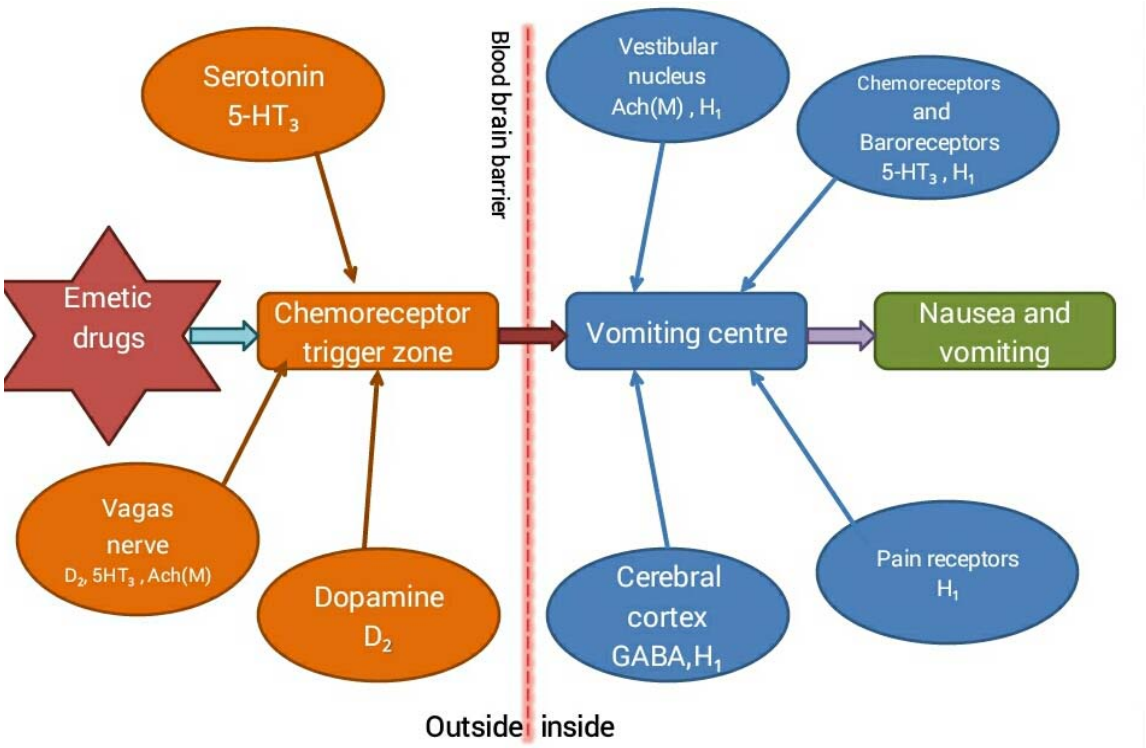


Fig. 1: This figure shows some of the factors that initiate vomiting and the neurotransmitter that involved in nausea and vomiting and where the antiemetic drugs involve to preventing nausea and vomiting

Author α ρ § ¥: Department of Pharmacognosy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
e-mails: sh_s@yahoo.com, adavoodi.pharm@gmail.com, azadbakht110@gmail.com, j.akbari@gmail.com
Author σ §: Traditinal and Complementary Medicine Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
e-mails: sadr128@gmail.com, azadbakht110@gmail.com
Author ω: Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
e-mail: e_salehifar@yahoo.com

Nausea and vomiting mechanism is complex. Excessive secretion of saliva occurs while nausea that shows the involvement of autonomic nervous system, so nausea is an event that involves a wide range of central nervous system and gastrointestinal tract [6].

There are two areas of the brain that are important in vomiting; the vomiting centre (VC) and the chemoreceptor trigger zone (CTZ) (Fig. 1). The VC makes network in parts of the brain stem and coordinates the actions of smooth muscles and skeletal functions involved in the vomiting [7, 8].

Persian medicine (PM) is a set of knowledge and practices used for the prevention, diagnosis and treatment of diseases [9]. This knowledge has been transferred from generation to generation since ancient times. World Health Organization (WHO) to implement the slogan "Health for all" is intended to develop traditional medicine, this decision was based on two fundamental: first, lack of people (up to 80% in some areas) to access primary health care and second, the lack of satisfaction with the treatment of modern medicine [10-13].

II. Factors that Initiate Vomiting

There are number of medicines to control of nausea and vomiting (Table 1) that with these antiemetic drugs, vomiting can be prevented in up to 70–80 % of patients [14]. Table 1 shows the modern drugs that use to treatment of nausea and vomiting.

III. Methods

In this article we used "comprehensive library of Islamic and traditional medicine software" and from about one thousands book we choose six important Persian Medicine (PM) book such as: Canon of medicine, Al-Abnieah, Tohfeh, Ekhtiarat, Al-shamel and Makhzan-ol-advieh. These books are written between 9-19 centuries. In other hand we searched Scopus, Pubmed, Google scholar and Science Direct for some of these plants that are effective in treatment of nausea and vomiting.

There are several terms that associated with nausea and vomiting in PM such as: “Ghe’y”, “Ghesyan”, “Tahavo”, and “Taghalobenaphs” refers to ‘’vomiting’’, ’’nausea’’, ‘’retching’’, and ’’permanent nausea’’, respectively. Herbal medicines specifications include: scientific, PM and common names, also their part(s) of used, some notifications and references that can use as drug to control of nausea and vomiting in PM were presented in this article.

IV. Results and Discussion

In this paper, we investigated six important books of Persian medicine and the result was about 126 plants that use for treatment of nausea and vomiting and in this paper 94 plants were presented.

Table 2 shows the plants that used for curing nausea and vomiting. This table sort by family name of plants and including data on the subject of: scientific name, PM name, and common name, part used, notice and the collection source.

Table 1: Modern drugs that use for treatment of nausea and vomiting

Line	Chemical class	Antiemetic drugs	Root	Neurotrans mitters	Rider	References
1	5-Hydroxy-tryptamine (5-HT3) antagonists	Ondansetron	Oral ,**IV	5-HT	Common side effect includes headaches, flushing, constipation/ diarrhea, malaise/ fatigue and bradycardias.	[15-17]
		Granisetron	Oral, IV, patch			
		Dolasetron	Oral, IV			
2	Steroids	Dexamethasone	IV	-	As Anti-nausea drug that is effective in *PONV and chemo-therapy	[18, 19]
3	Antihistamines	Cyclizine	Oral	Histamine	Pain while injecting and tachycardia limited it use. It often use in motion sickness. IV administration can cause tissue injury including: gangrene, burning.	[20-22]
		Promethazine	Oral, IV , ***IM			
4	Phenothiazines	Prochlorperizine	IV ,IM	Dopamine	Extra-pyramidal effect and sedation limited it use. Avoiding using in Parkinson’s patient.	[22-24]
		Perphenazine	IV			
5	Butyrophenones	Droperidol	IV, IM	Dopamine	It has the risk of sudden deaths because of long QT syndrome and torsades de pointes. 0.625-1.25 mg may be more effective for PONV	[25]

6	Benzamides	Metoclopramide	IV, IM , oral	Dopamine	Following in a single dose Extra-pyramidal side effects may occur up to 72 hours	[26]
7	Artimuscarinics	Hyoscine	IM, IV , SC, patch	Acetylcholine	-	[27]
8	NK_1	Aprepitant	Oral ,IV ,	Substance P	It use for nausea and vomiting induced by chemotherapy. It is effective for POVN	[28]
9	Cannabinoids	Nabilone	Oral	-	The effect of these two drugs are currently being investigated -they use in control of emetic induce by chemotherapy. They are not effective in PONV	[29-31]
		Tetrahydrocannabinol	IM, IV			

**PONV: Postoperative nausea and vomiting **IV: intravenous ***IM: intramuscular*

Table 2: The plants that used in Persian medicine to treatment of nausea and vomiting

Family	Scientific name	Persian Medicine name	Common name	Part(s) Used	Notice	References
Acanthaceae	*Justicia adhatoda*	Ajhose	Tentacle	Root	Its root can use for treatment of nausea	[32-34]
Alliaceae	*Allium cepa*	Bassal	Onion	Bulb	Cooking or fostering it with vinegar prevents nausea.	[32, 33, 35]
Anacardiaceae	*Mangifera indica*	Anbaj (anbeh)	Mango	Peduncle	Peduncle near the leaf with black pepper can stop vomiting.	[32, 33, 36]
	Pistacia intigerrima	Kakera	Crab's claw, Kakkar	Gall	It is more effective in vomiting.	[32, 33, 37]
	Pistacia lentiscus	Mastaci	Mastic	Resin	Drinking of it with appropriate spices use for treatment of vomiting.2.5 g of it with 450 g of water boil in a new pitcher until 1/3 of it remain, then drink it, if to be finished use a new pitcher, it use for treatment of emesis.	[32, 33, 38]
	Pistacia vera	Fastagh	Pistachio	Peel and kernel	Macerate external Green peel in water and drink it can prevent vomiting. It can prevent nausea and lock vomiting.	[32, 33, 39]
	Rhus coriria	Sumac	Sumac	Seed and leaf	Seed that be crushed with caraway-seed can calm emetic by drinking with cold water, in a person that always have emesis. (12.5 g of the syrup.) It remove/calm emetic.	[1, 32, 33]
Apiaceae (Umbelliferae)	*Anethum graveolens*	Shabat (shivid)	Dill	Leaf and seed	Eating its cooked leaves and seed remove nausea	[32, 33, 40]
	Apium graveolens	Karafs	Celery	Leaf, seed and root	Drinking 37.5 g of extract/7.5 g of it/ 12.5 g of cooked root, use for remove emesis. Drinking of leaf and root that mixed with honey can calm emesis.	[32, 33, 41]

	Carum carvi	Cumon	Caraway- seed	Seed	It can be effective in emesis.	[32, 33, 42]
	Carum copiticum	Nankhah	Aniseed, Bishop's weed	Seed	Up to 7.5 g to improve and calming of emesis.	[32, 33]
	Coriandrum sativum	Kazbareh	Coriander	Fruit	37.5 g of juice and 75-112.5 g of it can lock and remove emesis. When it combines with sumac can be more effective in preventing of vomiting. 5 g of it with 7.5 g of plantain water prevent vomiting.	[32, 33, 43]
	Cuminum cyminum	Keroya	Cumin	Seed	-up to 12.5 g of syrup to prevent vomiting.	[32, 33, 44]
	Foeniculum vulgare	Razianj	Fennel	Seed, root	Alone or with appropriate spice use for treatment of nausea. With cold water is effective for nausea with fever.	[32, 33, 45]
Asphodelaceae	*Aloe barbadensis, A. Littoralis*	Sabar	Aloe	Gel of outer leaf	It can prevent permanent nausea.	[32, 33, 46]
Asteraceae (compositae)	*Artemisia dracunculus*	Tarkhon	Tarragon	Aerial parts	It is gastrotonic and can prevents nausea and vomiting	[32, 33, 47]
	Onopordum acanthium	Dehamasa	Artichoke	Leaves, Root	It can calm vomiting	[32, 33, 48]
	Cichorium intybus	Handba	Chicory (Endive)	Leaf	Drinking of its extract use for treatment of vomiting. 225 g of juice use to calming emesis.	[32, 33, 49]
Berberidaceae	*Berberis asiatica*	Hazaz hendi	Chutro, Rasanjan	Fruit	It can calm vomiting.	[32, 33, 50]
	Berberis vulgaris	Emberbaris	Barberry	Fruit	75 g of Barberry juice prevent nausea.	[32, 33, 51]
Urticaceae	*Parietaria officinalis*	Azanofar	Wall palitory	Whole plant	Drinking of 5 g of syrup can calm nausea	[32, 33, 52]
Brassicaceae (Cruciferae)	*Descurainia sophia*	Khobbe	Hedge-mustard/ Garlic hedge-mustard	Seed	Decoction of its seed with water or rose water that drink 0.5 g of it warmly, can calm vomiting and if vomiting continue use it again until it stop	[32, 33, 53]

Burseaceae	*Boswellia sacra*	Condor	Frankincense (Oliban)	Oleogum resin	It use with Mastic for treatment of emesis. 1.25 g of syrup can lock vomiting. It can remove/prevent emesis.	[32, 33, 54]
Cannabaceae	*Cannabis sativa*	Ghanab	Hemo-seed	Seed	The seed of it can calm nausea.	[32, 33, 55]
	Humulus lupulus	Ashne	Bruon	Whole of plant	7.5 g of cooked plant lock/ remove emesis. It also can calm nausea It can lock and cut vomiting	[32, 33, 56]
Caricaceae	*Carica papaya*	Pepite	Papaw (papaya)	Fruit and latex	Drinking of it alone or with combination of appropriate spices, for vomiting that don't stop.	[32, 33, 57]
Cistaceae	*Cistus ladaniferus*	Lazan	Labdanum	oleo-resin	It use for preventing of nausea.	[32, 33, 58]
Combretacea	*Terminalia chebula*	Ahlije-kaboli	Myrobalan/ chebulic myrobalan	whole of plant	Whole of plant use for treatment of nausea.	[32, 33, 59]
Curcurbitaceae	*Cucurbita maxima, C.pepo*	Gharae	Winter quash	Fruit	It can prevent vomiting	[32, 33, 60]
Cycadaceae	*Cycas revoluta*	Jemar	Sago palm	Fruit	It can remove vomiting	[32, 33, 61]
Cyperaceae	*Cyperus longus*	Saed	Sedge/ Galingale	Roots and bark	2.5-10 g of syrup to cut vomiting. If chafed it, then put it a ceramic on the fire until dried, so eat some of it every morning, it in combination of *Pistacia atlantica* oil can cut vomiting. Poultice or drinkable of it cut vomiting.	[32, 33, 62]
Elaeagnaceae	*Elaeagnus angustifolia*	Ghabira	Oleaster/ Russian olive	Fruit	It can calm and lock vomiting. It is also effective in nausea.	[32, 33, 63]
Fagaceae	*Quercus ilex*	Ballot	Holm oak	fruit	It use for treatment of nausea.	[32, 33, 64]

Fumariaceae	*Fumaria parviflora*	Shahtaraj	Fumitory	Aerial parts	Fumitory with vinegar to treatment of emesis. 7.5-12.5 g of it/ 150-300 g of juice in combination of yellow myrobalan water that cooked with sugar, and in cooked 12.5-25 g of it/12.5 g of seed can be effective in emesis. If it mixed with vinegar, can calm emesis.	[32, 33, 65]
Hypericaceae	*Hypericum perforatum*	Naksir	St john's wort	Flower	It removes vomiting.	[32, 33, 66]
Labiatae (Lamiaceae)	*Thymus serpyllum*	Sisanber-nemam	Wild thyme	Seed, Aerial part	Drinking seed with wine can prevent emesis. Drinking it with vinegar use for treatment of bloody vomiting. 5 g of syrup can use for treatment of vomiting.	[32, 33, 67]
	Mentha aquatica	Fodanj	Pennyroyal	Aerial parts	Up to 5 g of syrup use for remove of emesis. If it used with vinegar, can calm nausea and vomiting. Its combination with syrup of pomegranate use for remove of emesis.	[32, 33, 68]
	Mentha piperita	Na'na	Mint	Leaf and peduncle	Drinking 2-3 peduncles with sour pomegranate juice for treatment of emesis. It is effective in the vomiting.	[32, 33, 69]
	Ocimum basilicum	Franjmeshk	Common calamint	Aerial parts	It can prevent nausea.	[32, 33, 70]
	Teucrium montanum	Marmahooz	Marram/ marum	Leaf, flower and seed	5 g of leaf, seed and flower syrup and 37.5 g of juice calm and prevent emesis.	[32, 33, 71]
	Satureja hortensis	Satar	Summer savory	Leaves	Eating it is more effective in nausea. Drinking cooked juice of it with purgative spices for treatment of nausea	[32, 33, 72]
Lauraceae	*Sassafras albidum*	Sasaferas	Sassafras	Root bark	It can remove emesis.	[32, 33, 73]
Leguminosae (Fabaceae)	*Acacia arabica*	aghaghia	Locust/acacia	Gum	It is effective in nausea and it also can lock vomiting	[32, 33, 74]
	Alhagi camelorum, A. mauroroum	Taranjebin	Hedysarum	Manna	It use for treatment of nausea.	[32, 33, 75]

	Tamarindus indica	Tamr hendi	Tamarind	Fruit	35- 150 g of syrup can calm nausea. It is effective in vomiting and prevents vomiting with astringent effect. Note: do not macerate tamarind for a long time, because it can cause emetic.	[32, 33, 76]
	Trigonella corniculata	Handeghoghi bostani	Cultivated fenugreek	Fruit	It can effective in nausea	[32, 33, 77]
	Vicia faba	Baghala	Faba bean/Broad bean	Fruit	It removed vomiting	[32, 33, 78]
Lythraceae	*Punica granatum*	Romane hamez	Pomegranate	Flowers and fruit	Juice and wine of fruit can prevent vomiting. Crushed sour pomegranate with currant and cumin can exterminate vomiting. It can cut vomiting.	[32, 33, 79]
Malvaceae	*Adansonia digitata*	Habhabo	Baobab	Fruit	2.5 g of syrup cut emesis	[32, 33, 80]
Meliaceae	*Melia azedarach*	Azad derakht	Bead tree/ Persian lilac/ china berry/Azedarach	Leaf, flower, root	Drinking of extract can prevent nausea. Poultice of leaf on stomach can calm nausea.	[32, 33, 81]
Moraceae	*Morus alba, M. nigra*	Toot hamez	Mulberry	Fruit	It can lock vomiting.	[32, 33, 82]
Moringaceae	*Moringa arabica/ M. pterygosperma*	Habo roman	Horseradish Tree	Seed	Oil of seeds with Mastic use for vomiting. 5 g of syrup of it can be effective in emesis.	[32, 33, 83]
Myristicaceae	*Myristica fragrans*	Jozeboa	Mace	Fruit	Up to 10 g of syrup prevent/remove emesis. Note: great use of it can cause immorality	[32, 33, 84]
Myrtaceae	*Eugenia caryophyllata*	Gharanfol	Clove	Flower	Up to 5 g of syrup can be effective in remove/ calm of emesis. It is more effective in emesis.	[32, 33, 85]
	Myrtus Communis	Ase	Common Myrtle	Seed	Juice of seed can calm vomiting. Drinking of seeds syrup and its extract is effective in prevent vomiting.	[32, 33, 86]
Oxalidaceae	*Oxalis acetosella*	Hemaz	Clover	Flower, Leaf	45 g of syrup calming, curing and remove emesis. Note: the kind of it that grows near water is effective in nausea.	[32, 33, 87]

Papilionaceae	*Lupinus termis, L. angustifolia*	Tarmas	Lupine	Seed, Leaves	It can calm nausea and prevent vomiting.	[32, 33, 88]
Phyllanthaceae	*Phyllanthus emblica*	Amlaj/ Shiramlaj	Emblic	Fruit	7.5-12.5 g of plant and 25 g of it cooked can prevent vomiting. Macerate Emblic in milk can prevent vomiting. It can calm vomiting and cut it.	[32, 33, 89]
Piperaceae	*Piper longum*	Pipal/ darolfelfel	Pepper	Leaf	Burn the dried leaf (7 pieces) that felt of tree, transfer it rapidly to cold water; then drink the water, this can prevent emesis 5 g of syrup remove vomiting. Its water macerate extract can prevent emesis.	[32, 33, 90]
Poaceae (Gramineae)	*Agropyron repens*	Dop/ Bidgiahe	Couch grass	Leaf and peduncle	Drinking of leaf extract and thin peduncle that washed with white rice and chafe with each other in combination of crystallised sugar, can remove vomiting.	[32, 33, 91]
	Andropogon schoenanthus	Azkhar	Lemon grass	Root, Flower bloom	5g of it alone or combination with pepper use for treatment and calming of nausea. It use for calming vomiting.	[32, 33, 92]
	Cynodon dactylon	Sile/ Margh/ Bidgiahe	Bermuda grass	Seed and root	Its seed extract cut vomiting.	[32, 33, 93]
	Hordeum vulgare	Shaeer	Barley	Seed	Flour of the barley with juice of pomegranate use for treatment of vomiting. Give time (one night) to dough of the barley to turn acid then eat 37.5-45.0 g of it can use for treatment of vomiting. Flour of it is effective in treatment of vomiting	[32, 33, 94]
	Panicum miliaceum	Dakhan/ Arzan	Broomcorn/hog millet red/broom tail/ millet	Seed	Flour of it can cut vomiting.	[32, 33, 95]
	Saccharum spontaneum	Tabashir	Tabasheer	Stem	5 g of syrup cut vomiting	[32, 33, 96]
	Oryza sativa	Orz / brenj	Rice	seed	It combination with fresh yogurt diluted with water and sumac can calm nausea. 75 g of grilled rice that macerate in water (200-250 g) at night then drink the filtrate of it, this can remove nausea.	[32, 33, 97]

Polygonaceae	*Polygonum bistorta*	Anjbar	Bistort	Leaf/whole of plant	5 g of distillates (syrup)/ 2.5 g of extract / 12.5 g of leaf is effective in treatment of emesis. 5 g of half-bruised of it that boiling with sugar can cut vomiting. It can calm vomiting.	[32, 33, 98]
	Polygonum aviculare	Asioraei	Knotgrass	Aerial part	350 g of syrup lock /cut vomiting.	[32, 33, 99]
	Rheum ribes	Ribas	Syrian Rhubarb	Whole plant	Up to75 g of syrup remove/lock vomiting. It can calm nausea). Note: Inspissated juice is much stronger than juice of it.	[32, 33, 100]
Portulacaceae	*Portulaca oleracea*	Baghlat ol hamgha	Portulaca	Leaf, seeds and peduncle	It can calm and prevent vomiting.	[32, 33, 94]
Ranunculaceae	*Nigella sativa*	Shoniz	Negella seeds/ ergot of rye	seed	It use for treatment of nausea.	[32, 33, 101]
	Thalictrum foliolosum	Piaranga	Meadow-rue	Root, Aerial part	1/3 of it with 2/3 of black pepper that bruised with each other, then tablet it of the required size of pea and use one of it in the morning and the other at night	[32, 33, 102]
Rhamnaceae	*Zizyphus sativa*	Onabe	Jujube	Leaf	Chew the leave can use for treatment of emesis.	[32, 33, 94]
Rosaceae	*Amygdalus communis var. amara*	Lozolmare/ Lose bari and lose jabali	Almond	Flower and fruit	Up to 7.5 g of syrup and up to 5 g of flower remove vomiting. 10 g of flower syrup and15 g of fruit syrup can remove vomiting	[32, 33, 94]
	Crataegus azarolus	Zaeror	Hawthorn	Fruit	62.5 g of juice and 30 g of fruit calm and lock vomiting.	[32, 33, 103]
	Cerasus vulgaris	Gharasia (Albalo)	Cherry	Fruit	It can cut emesis and remove vomiting.	[32, 33, 104]
	cydonia vulgaris	Safar jal	Quince	Fruit	Inspissated juice (up to 20 g) of sour fruit remove and cut vomiting. Smell of it can prevent emesis With leaf of spearmint use for prevention of emesis. Use up to75 g of juice of it cut vomiting. It and its extract prevent vomiting. Also it can prevent nausea.	[32, 33, 105]

	Malus domestica	Toffah	Apple	Fruit	35 g of Inspissated juice of fruit without sweeting can prevalence nausea. Dried/flour fruit with pomegranate juice and other appropriate spices can reduce vomiting. Flour of apple prevented emesis. Chew it with honey calm vomiting. It also can prevent nausea. Sour of apple can calm vomiting.	[32, 33, 106]
	Pyrus communis	Kamsari	Pear	Whole of plant	Inspissated juice locks vomiting. It can prevent emesis. It can lock vomiting.	[32, 33, 107]
	Prunus cerasifera	Ejas/ Adrak/ Shamloj	Damson	Fruit	225 g of syrup is effective/calm and prevent vomiting. The sour of it can be effective in nausea. 5 g of it in combination with 5 g pepper can remove nausea. Green damson can cut vomiting.	[32, 33, 108]
	Rosa canina	Nasrin	Jonquil	Petal	It use for treatment of vomiting.	[32, 33, 109]
Rutaceae	*citrus aurantium var.amara*	Naranj	Sour orange	Fruit	Drinking 3.75 g of dried fruit with warm water use for treatment of emesis. Sour of it can calm vomiting.	[32, 33, 110]
	Citrus limonum var.dulicis	Lemon	Lemon	Fruit	Sour of lemon use for treatment of vomiting.	[32, 33, 111]
	Citrus medica var. cedrata	Otroj	Citron	Fruit and peel	12.5 g of dried /25 g of jam can reduce vomiting. Peel that cooked can be effective in vomiting, and the yellow peel can cure nausea. Sour water of it can calm and reduce vomiting. Inspissated juice of citron is much effective than Inspissated juice of unripe grapes in cutting vomiting.	[32, 33, 112]
	Citrus sinensis	Konle	Orange	Peel, seed and Fruit	Its syrup is very useful in nausea and vomiting	[32, 33, 113]
	Aegle marmelos	Bal	Golden/ stone/ wood apple, Bengal quince	Seed/ fruit	It is effective and prevent vomiting	[32, 33, 114]
Sapindaceae	*Sapindus trifoliatus*	Ratte	Soapnut	Fruit	It can useful in nausea	[32, 33, 115]
Solanaceae	*Solanum melongena*	Badamjan	Egg-plant	Fruit	Eating grill fruit can remove vomiting in person who had nausea after eating food.	[32, 33, 116]

Thymelaeaceae	*Agallochum malaccense*	Ood	Aloes-wood/ Lute	Stem	It's burned and combination with milk can calm vomiting. It also can prevent nausea	[32, 33, 117]
Valerianaceae	*Valeriana dioscorides*	Sonbol kohi	valerian	Rhizome	Up to 5 g of syrup lock/prevent vomiting. With cold water use for treatment/prevent of nausea.	[32, 33, 118]
	Valeriana jatamansi	Sonbol tibe	Valerian	Roots	Up to 5 g of syrup lock vomiting.	[32, 33, 119]
Vitaceae	*Vitis vinifera*	Feghaho kerm/ kerm	Grapevine	Fruit	-it cut vomiting and bloody vomiting. -syrup of it that Inspissated with sugar can calm nausea -drinking its syrup can prevent nausea and lock vomiting. Note: it's juice is more effective that it	[32, 33, 120]
Zingiberaceae	*Zingiber zerumbet*	Zaranbad	Coriande	root	5 g of syrup lock emesis. Keeping it in mouth can cut vomiting.	[32, 33, 121]
	Elettaria cardamomum	Ghaghale/ Abale	Cardamom	seed	2.5-5 g of syrup can lock vomiting. It can be calming, remove and effective in nausea. (it also can prevent vomiting) If drink its extract with it' bark in combination of vinegar can calm emesis. Use it with mastic juice and pomegranate juice for treatment of emesis. Boiling half-bruised with peel in water or rose-water use for treatment of emesis. It is more effective in treatment of emesis especially while eat with peel.	[32, 33, 122]

V. Herbal Remedies have been used in the Literature for the Treatment of Nausea and Vomiting

a) Lemon (Citrus Lemon)

Rutaceae are a great family that has about 1800 species in 160 genera. Essential oil of C. lemon that was extracted with hydro-distillation includes volatile (%85-99) and non-volatile (%1-15). Chemical constituents that identified in C. lemon essential oils are: Limonene (it is the major compound in citrus peels), limonene oxide, α-terpineol, carvone, carveol, eugenol, spathulenol, caryophyllene oxide, α-terpineol, 3-cyclohexane-1-methanol. A study was conducted to evaluate the effect of aromatherapy essential oils in the control of nausea and vomiting associated with pregnancy. The study was conducted on 100 pregnant women showed that inhaling lemon can be effective in reducing nausea and vomiting in pregnancy.

A study on 180 people in three groups: control group, treated with intramuscular inject of metoclopramide and was treated with lemon peel; results showed that the group who were treated with lemon peel their symptoms were better control.

In a study of 50 women who had undergone caesarean section and vaginal deliveries has been shown that nausea and vomiting in group that used Lemon peel is significantly lower than the control group.

In addition, nasal spray formulation of lemon essential oil (that extracted from peel of Citrus sinensis) has been showed significant effects on the control of nausea and vomiting [123-126].

b) Berberis (Berberis Vulgaris)

Barberry has about 500 species around the world. Berberine and berbamine are the main constituents that found in different species of Barberry. There are several pharmacological and biological effect for *B. vulgaris* such as: antihistaminic and anticholinergic. These two effects can be helping the improvement of nausea and vomiting [127, 128].

c) Apple (Malus Domestica)

There are about 100 varieties of apples commercially. Apples contain flavonoids, fibre, pectin, high potassium, low sodium, zero of fat. In a study on 19 patients treated by cisplatin showed that eating three times a day from a diet that includes: vanilla ice cream, cheese and apple sauce can be effective to control nausea and vomiting in this category of people [129, 130].

d) Peppermint (Mentha Piperita)

The result of GC–MS analysis of essential oils from hydro-distillation extract of *Menthe piperita* showed that there are many compounds in the essential oil, such as: camphene, sabinene, β-pinene, α-terpinene, limonene, terpinolene, p- cymene, menthone, menthol, γ-terpineole, trans-carveol, carvone, pipertitone oxide, and β-caryophllene. Peppermint oil can be effective in controlling nausea and vomiting that caused by chemotherapy. In a study in patients with gynecologic surgery, was shown that peppermint is very effective in reducing nausea and vomiting after surgery.

In another study in 123 patients who is undergoing cardiac surgery, shown that the use of nasal inhaler of peppermint oil can be useful in controlling nausea and vomiting after cardiac surgery [131-133].

e) Valerian (Valeriana Jatamansi)

Valerian is scattered around worldwide with about 250 species. Valerian contains more than 150 chemical compounds such as; pyridine alkaloids, organic acids and terpenes, in particular valepotriates and esterifies iridoid-monoterpenes, but the main three chemicals that are active are the essential oils, valerenic acid and valenol, valepotriates, and a few alkaloids.

A study about antiemetic effects of *V. officinalis* in chickens has been studied against nausea and vomiting that induced by copper sulphate. The results indicate that valerian has significant effect on the control of nausea and vomiting [134-136].

f) Ginger (Zingiber Officinale)

Ginger liquid and capsules preparations are a herbal medications used to control nausea and vomiting due to chemotherapy, postoperative and pregnancy. Ginger extract because of gingerols and shogaol, effects on stimulate gastric contractions. These effects mainly occur by involving serotonergic 5-HT and 5-HT receptors and cholinergic M receptors [122, 137, 138].

VI. Conclusion

Since nausea and vomiting affect the quality of life and in many patients despite the use of antiemetic agent. We also seen these symptoms, so need for further investigation of the discovery of new drugs is felt, therefore, use the traditional medicine can help us do towards to this goal.

Conflict of Interest Statement

We declare that we have no conflict of interest.

References Références Referencias

1. Nazari M, Taghizadeh A, Orafaei H, Rakhshandeh H, Bazzaz MM. Nausea and vomiting in Iranian Traditional Medicine based on Avicenna's viewpoint. Electronic physician. 2015; 7(2): 1047.
2. Darvall J, Handscombe M, Leslie K. Chewing gum for the treatment of postoperative nausea and vomiting: a pilot randomized controlled trial. British Journal of Anaesthesia. 2017; 118(1): 83-9.
3. Pasricha PJ, Colvin R, Yates K, Hasler WL, Abell TL, Ünalp–Arida A, et al. Characteristics of patients with chronic unexplained nausea and vomiting and normal gastric emptying. Clinical Gastroenterology and Hepatology. 2011; 9(7): 567-76. e4.
4. Pleuvry BJ. Physiology and pharmacology of nausea and vomiting. Anaesthesia & Intensive Care Medicine. 2015; 16(9): 462-6.
5. Kenward H, Pelligand L, Savary-Bataille K, Elliott J. Nausea: Current knowledge of mechanisms, measurement and clinical impact. The Veterinary Journal. 2015; 203(1): 36-43.
6. Iqbal IM, Spencer R. Postoperative nausea and vomiting. Anaesthesia & Intensive Care Medicine. 2012; 13(12): 613-6.
7. Navari RM. Management of chemotherapy-induced nausea and vomiting. Drugs. 2013; 73(3): 249-62.
8. Apfel C, Heidrich F, Jukar-Rao S, Jalota L, Hornuss C, Whelan R, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. British journal of anaesthesia. 2012; 109(5): 742-53.
9. Amirian T, Maddahi Z, Azadbakht M, Yousofpour M. A Comparative Study on the Views of Persian Medicine and Conventional Medicine about Thirst and its Etiology. Journal of Mazandaran University of Medical Sciences. 2016; 26(139): 246-57.
10. Rezaeizadeh H, Alizadeh M, Naseri M, Ardakani MS. The Traditional Iranian Medicine Point of View on Health and. Iranian J Publ Health. 2009; 38(1): 169-72.
11. Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. The Journal of Alternative and Complementary Medicine. 2009; 15(3): 243-6.
12. Ensiyeh J, Sakineh M-AC. Comparing ginger and vitamin B6 for the treatment of nausea and vomiting

in pregnancy: a randomised controlled trial. Midwifery. 2009; 25(6): 649-53.
13. Bodeker G, Kronenberg F. A public health agenda for traditional, complementary, and alternative medicine. American journal of public health. 2002; 92(10): 1582-91.
14. Chan A, Low XH, Yap KY-L. Assessment of the relationship between adherence with antiemetic drug therapy and control of nausea and vomiting in breast cancer patients receiving anthracycline-based chemotherapy. Journal of Managed Care Pharmacy. 2012; 18(5): 385-94.
15. Ryu J, So Y-M, Hwang J, Do S-H. Ramosetron versus ondansetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surgical endoscopy. 2010; 24(4): 812-7.
16. Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM, Group SS. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. Supportive Care in Cancer. 2011; 19(10): 1609-17.
17. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Supportive Care in Cancer. 2014; 22(2): 469-77.
18. Aapro M, Fabi A, Nole F, Medici M, Steger G, Bachmann C, et al. Double-blind, randomised, controlled study of the efficacy and tolerability of palonosetron plus dexamethasone for 1 day with or without dexamethasone on days 2 and 3 in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy. Annals of oncology. 2010; 21(5): 1083-8.
19. De Oliveira Jr GS, Castro-Alves LJS, Ahmad S, Kendall MC, McCarthy RJ. Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. Anesthesia & Analgesia. 2013; 116(1): 58-74.
20. Anderka M, Mitchell AA, Louik C, Werler MM, Hernández-Diaz S, Rasmussen SA. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Research Part A: Clinical and Molecular Teratology. 2012; 94(1): 22-30.
21. McDevitt L, Mowat I. Transient paralysis after cyclizine administration. Anaesthesia. 2013; 68(10): 1084-.
22. Becker DE. Nausea, vomiting, and hiccups: a review of mechanisms and treatment. Anesthesia progress. 2010; 57(4): 150-7.
23. Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. Journal of the National Comprehensive Cancer Network. 2012; 10(4): 487-92.
24. Schnabel A, Eberhart LH, Muellenbach R, Morin AM, Roewer N, Kranke P. Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review. European Journal of Anaesthesiology (EJA). 2010; 27(12): 1044-51.
25. Schaub I, Lysakowski C, Elia N, Tramèr MR. Low-dose droperidol (≦ 1 mg or≦ 15 μg kg− 1) for the prevention of postoperative nausea and vomiting in adults: quantitative systematic review of randomised controlled trials. European Journal of Anaesthesiology (EJA). 2012; 29(6): 286-94.
26. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Supportive Care in Cancer. 2013; 21(6): 1655-63.
27. Apfel CC, Zhang K, George E, Shi S, Jalota L, Hornuss C, et al. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. Clinical therapeutics. 2010; 32(12): 1987-2002.
28. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Supportive Care in Cancer. 2010; 18(4): 423-31.
29. Ware MA, Fitzcharles M-A, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia & Analgesia. 2010; 110(2): 604-10.
30. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. British journal of pharmacology. 2011; 163(7): 1411-22.
31. Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. Supportive Care in Cancer. 2011; 19(10): 1533-8.
32. Aghili Khorasani M. Makhzan-advieh. second ed: Tehran university of medical science. 1390: 1-400.
33. Avisenna M. The canon of medicine. (Sharafkandi A, trans), [in Persian] Tehran. 1997; 2: 190-3.
34. Tambekar D, Tiwari B, Shirsat S, Jaitalkar D. Antimicrobial potential and Phytochemical analysis of medicinal plants from lonar lake. International Journal of Lifescience Biotechnology and Pharmaceutivcal Research. 2013; 2(3): 203-2011.
35. Kendler BS. Garlic (Allium sativum) and onion (Allium cepa): a review of their relationship to cardiovascular disease. Preventive medicine. 1987; 16(5): 670-85.

36. Rajith N, Navas M, Thaha AM, Manju M, Anish N, Rajasekharan S, et al. A study on traditional mother care plants of rural communities of South Kerala. Indian Journal of Traditional Knowledge. 2010; 9(1): 203-8.
37. Jain S, Puri H. Ethnomedicinal plants of jaunsar-bawar hills, uttar pradesh, india. Journal of Ethnopharmacology. 1984; 12(2): 213-22.
38. Dabos KJ, Sfika E, Vlatta LJ, Frantzi D, Amygdalos GI, Giannikopoulos G. Is Chios mastic gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial. Journal of ethnopharmacology. 2010; 127(2): 205-9.
39. Sadeghpour O, Mohammadi A, Aliasl J. Eeffective herbal medicines on Nausea and vomiting based on Canon of Avecina. Advances in Environmental Biology. 2015; 9(3): 557-60.
40. Heidarifar R, Mehran N, Heidari A, Koohbor M, Mansourabad MK. Effect of Dill (Anethum graveolens) on the severity of primary dysmenorrhea in compared with mefenamic acid: A randomized, double-blind trial. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2014; 19(4): 326.
41. Shivashri C, Rajarajeshwari T, Rajasekar P. Hepatoprotective action of celery (Apium graveolens) leaves in acetaminophen-fed freshwater fish (Pangasius sutchi). Fish physiology and biochemistry. 2013; 39(5): 1057-69.
42. Thompson Coon J, Ernst E. Herbal medicinal products for non-ulcer dyspepsia. Alimentary pharmacology & therapeutics. 2002; 16(10): 1689-99.
43. Rajeshwari U, Andallu B. Medicinal benefits of coriander (Coriandrum Sativum L). Spatula DD. 2011; 1(1): 51-8.
44. Zaidi SFH, Yamada K, Kadowaki M, Usmanghani K, Sugiyama T. Bactericidal activity of medicinal plants, employed for the treatment of gastrointestinal ailments, against Helicobacter pylori. Journal of Ethnopharmacology. 2009; 121(2): 286-91.
45. Jahromi BN, Tartifizadeh A, Khabnadideh S. Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. International Journal of Gynecology & Obstetrics. 2003; 80(2): 153-7.
46. Husain SZ, Malik RN, Javaid M, Bibi S. Ethonobotanical properties and uses of medicinal plants of Morgah biodiversity park, Rawalpindi. Pak J Bot. 2008; 40(5): 1897-911.
47. De Pradier E. A trial of a mixture of three essential oils in the treatment of postoperative nausea and vomiting. International Journal of Aromatherapy. 2006; 16(1): 15-20.
48. Ahmad H, Khan SM, Ghafoor S, Ali1 N. Ethnobotanical study of upper siran. Journal of herbs, spices & medicinal plants. 2009; 15(1): 86-97.
49. C Verster J, Penning R. Treatment and prevention of alcohol hangover. Current drug abuse reviews. 2010; 3(2): 103-9.
50. Kunwar RM, Mahat L, Acharya RP, Bussmann RW. Medicinal plants, traditional medicine, markets and management in far-west Nepal. Journal of ethnobiology and ethnomedicine. 2013; 9(1): 1.
51. Cheng K-C, Li Y-X, Cheng J-T. The use of herbal medicine in cancer-related anorexia/cachexia treatment around the world. Current pharmaceutical design. 2012; 18(31): 4819-26.
52. Passàli D, Damiani V, Passàli FM, Passàli GC, Bellussi L. Nasal obstruction and headache: A real correlation? International journal of pediatric otorhinolaryngology. 2004; 68(11): 1407-11.
53. Farooq S, Barki A, Khan MY, Fazal H. Ethnobotanical studies of the flora of tehsil Birmal in South Waziristan Agency, Pakistan. Pakistan Journal of Weed Science Research. 2012; 18(3): 277-91.
54. Al-Harrasi A, Al-Saidi S. Phytochemical analysis of the essential oil from botanically certified oleogum resin of Boswellia sacra (Omani Luban). Molecules. 2008; 13(9): 2181-9.
55. Machado Rocha FC, Stefano S, De Cassia Haiek R, Rosa Oliveira L, Da Silveira D. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. European journal of cancer care. 2008; 17(5): 431-43.
56. Van Cleemput M, Cattoor K, De Bosscher K, Haegeman G, De Keukeleire D, Heyerick A. Hop (Humulus lupulus)-derived bitter acids as multipotent bioactive compounds. Journal of natural products. 2009; 72(6): 1220-30.
57. Kovendan K, Murugan K, Kumar AN, Vincent S, Hwang J-S. Bioefficacy of larvicdial and pupicidal properties of Carica papaya (Caricaceae) leaf extract and bacterial insecticide, spinosad, against chikungunya vector, Aedes aegypti (Diptera: Culicidae). Parasitology research. 2012; 110(2): 669-78.
58. Feistel B, Walbroel B. Cistus extract containing enriched secondary plant ingredients. Google Patents; 2015.
59. Balachandran P, Govindarajan R. Cancer—an ayurvedic perspective. Pharmacological research. 2005; 51(1): 19-30.
60. Di Stasi L, Oliveira G, Carvalhaes M, Queiroz-Junior M, Tien O, Kakinami S, et al. Medicinal plants popularly used in the Brazilian Tropical Atlantic Forest. Fitoterapia. 2002; 73(1): 69-91.
61. Mandal SM, Migliolo L, Das S, Mandal M, Franco OL, Hazra TK. Identification and characterization of a bactericidal and proapoptotic peptide from Cycas

revoluta seeds with DNA binding properties. Journal of cellular biochemistry. 2012; 113(1): 184-93.
62. Shahbazi Y, Shavisi N, Karami N, Kakaei S. Chemical composition and in vitro antibacterial activity of Ferulago angulata (Schlecht.) Boiss essential oil. Pharmaceutical Sciences. 2015; 21(1): 6.
63. Karimi G, Hosseinzadeh H, Rassoulzadeh M, Razavi BM, Taghiabadi E. Antinociceptive effect of Elaeagnus angustifolia fruits on sciatic nerve ligated mice. Iranian Journal of Basic Medical Sciences. 2010; 13(3): 97-101.
64. Romagnoli E, Barboni T, Santoni P-A, Chiaramonti N. Quantification of volatile organic compounds in smoke from prescribed burning and comparison with occupational exposure limits. Natural Hazards and Earth System Sciences. 2014; 14(5): 1049-57.
65. Ghani A, Ali Z, Perveen S. Folk Recipes and Ethnobotanical Survey of Medicinal Plants Mianwali District (Pakistan). Int J Curr Pharm Res. 2012; 4(2): 61-3.
66. Solomon D, Adams J, Graves N. Economic evaluation of St. John's wort (Hypericum perforatum) for the treatment of mild to moderate depression. Journal of affective disorders. 2013; 148(2): 228-34.
67. Raju NJ, Avinash C, Suresh P. Evaluation of in vitro Anthelmintic Activity of Seed Extract of Thymus serpyllum. Indo American Journal of Pharmaceutical Research. 2015; 5(3): 1230-3.
68. Anderson W, Barrows M, Lopez F, Rogers S, Ortiz-Coffie A, Norman D, et al. Investigation of the anxiolytic effects of naringenin, a component of Mentha aquatica, in the male Sprague-Dawley rat. Holistic nursing practice. 2012; 26(1): 52-7.
69. Lane B, Cannella K, Bowen C, Copelan D, Nteff G, Barnes K, et al. Examination of the effectiveness of peppermint aromatherapy on nausea in women post C-section. Journal of Holistic Nursing. 2012; 30(2): 90-104.
70. Zhang J-W, Li S-K, Wu W-J. The main chemical composition and in vitro antifungal activity of the essential oils of Ocimum basilicum Linn. var. pilosum (Willd.) Benth. Molecules. 2009; 14(1): 273-8.
71. Stanković MS, Stefanović O, Čomić L, Topuzović M, Radojević I, Solujić S. Antimicrobial activity, total phenolic content and flavonoid concentrations of Teucrium species. Central European Journal of Biology. 2012; 7(4): 664-71.
72. Babajafari S, Nikaein F, Mazloomi SM, Zibaeenejad MJ, Zargaran A. A review of the benefits of Satureja species on metabolic syndrome and their possible mechanisms of action. Journal of evidence-based complementary & alternative medicine. 2015; 20(3): 212-23.
73. Laudato M, Capasso R. Useful plants for animal therapy. OA Alternative Medicine. 2013; 1(1): 1-6.
74. Ahmad M. Checklist of medicinal flora of tehsil Isakhel, district Mianwali-Pakistan. Ethnobotanical Leaflets. 2006; 2006(1): 4.
75. Khan FM. Ethno-veterinary medicinal usage of flora of greater Cholistan desert (Pakistan). Pak Vet J. 2009; 29(2): 75-80.
76. Havinga RM, Hartl A, Putscher J, Prehsler S, Buchmann C, Vogl CR. Tamarindus indica L.(Fabaceae): patterns of use in traditional African medicine. Journal of ethnopharmacology. 2010; 127(3): 573-88.
77. Bajpai M, Mishra A, Prakash D. Antioxidant and free radical scavenging activities of some leafy vegetables. International journal of food sciences and nutrition. 2005; 56(7): 473-81.
78. Nasiri E, Hosseinimehr SJ, Azadbakht M, Madani SA. A review of natural products for burn healing based on the Iranian traditional medicine. J Mazandaran Univ Med Sci. 2014; 23: 263-80.
79. Bhandari PR. Pomegranate (Punica granatum L). Ancient seeds for modern cure? Review of potential therapeutic applications. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2012; 2(3): 171.
80. Osman MA. Chemical and nutrient analysis of baobab (Adansonia digitata) fruit and seed protein solubility. Plant Foods for Human Nutrition. 2004; 59(1): 29-33.
81. Shekarchian A, Etemad V, Bihamta MR, Assareh MH. Effects of salicylic acid on physiological traits of myrtle seedlings in salt stress condition. Advances in Environmental Sciences. 2016; 8(1).
82. Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of Iranian medicinal plants useful in diabetes mellitus. Arch Med Sci. 2008; 4(3): 285-92.
83. Medhi B, Khanikor H, Lahon L, Mohan P, Barua C. Analgesic, anti-inflammatory and local anaesthetic activity of Moringa pterygosperma in laboratory animals. Pharmaceutical biology. 2003; 41(4): 248-52.
84. Chung J, Choo J, Lee M, Hwang J. Anticariogenic activity of macelignan isolated from Myristica fragrans (nutmeg) against Streptococcus mutans. Phytomedicine. 2006; 13(4): 261-6.
85. Chaieb K, Hajlaoui H, Zmantar T, Kahla-Nakbi AB, Rouabhia M, Mahdouani K, et al. The chemical composition and biological activity of clove essential oil, Eugenia caryophyllata (Syzigium aromaticum L. Myrtaceae): a short review. Phytotherapy research. 2007; 21(6): 501-6.
86. Alipour G, Dashti S, Hosseinzadeh H. Review of pharmacological effects of Myrtus communis L. and its active constituents. Phytotherapy Research. 2014; 28(8): 1125-36.

87. Berg H. Differential seed dispersal in Oxalis acetosella, a cleistogamous perennial herb. Acta Oecologica. 2000; 21(2): 109-18.
88. Abdel-Monaim M, Abo-Elyousr K, Morsy K. Effectiveness of plant extracts on suppression of damping-off and wilt diseases of lupine (Lupinus termis Forsik). Crop protection. 2011; 30(2): 185-91.
89. Liu X, Zhao M, Wang J, Yang B, Jiang Y. Antioxidant activity of methanolic extract of emblica fruit (Phyllanthus emblica L.) from six regions in China. Journal of Food Composition and Analysis. 2008; 21(3): 219-28.
90. Sunila E, Kuttan G. Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. Journal of ethnopharmacology. 2004; 90(2): 339-46.
91. Al-Snafi A. Chemical constituents and pharmacological importance of Agropyron repens–A review. Research Journal of Pharmacology and Toxicology. 2015; 1(2): 37-41.
92. Negrelle R, Gomes E. Cymbopogon citratus (DC.) Stapf: chemical composition and biological activities. Rev Bras Pl Med. 2007; 9(1): 80-92.
93. Singh SK, Kesari AN, Gupta RK, Jaiswal D, Watal G. Assessment of antidiabetic potential of Cynodon dactylon extract in streptozotocin diabetic rats. Journal of Ethnopharmacology. 2007; 114(2): 174-9.
94. Fakhri M, Azadbakht M, Yousefi SS, Mousavinasab SN, Farhadi R, Azadbakht M. Medicinal Plants for Treatment of Neonatal Jaundice by Community of Attars (Traditional Healers) of Several Urban Areas in Mazandaran Province, Northern of Iran. British Journal of Medicine and Medical Research. 2016; 14(11).
95. Hu X, Wang J, Lu P, Zhang H. Assessment of genetic diversity in broomcorn millet (Panicum miliaceum L.) using SSR markers. Journal of Genetics and Genomics. 2009; 36(8): 491-500.
96. Chandel AK, Narasu ML, Chandrasekhar G, Manikyam A, Rao LV. Use of Saccharum spontaneum (wild sugarcane) as biomaterial for cell immobilization and modulated ethanol production by thermotolerant Saccharomyces cerevisiae VS 3. Bioresource technology. 2009; 100(8): 2404-10.
97. Morekian R, Mirlohi M, Azadbakht L, Maracy MR. Heavy metal distribution frequency in Iranian and imported rice varieties marketed in central Iran, Yazd, 2012. International Journal of Environmental Health Engineering. 2013; 2(1): 36.
98. Starr Ge, Oberbauer SF, Pop E. Effects of lengthened growing season and soil warming on the phenology and physiology of Polygonum bistorta. Global Change Biology. 2000; 6(3): 357-69.
99. Hsu C-Y. Antioxidant activity of extract from Polygonum aviculare L. Biological Research. 2006; 39(2): 281-8.
100. Öztürk M, Aydoğmuş-Öztürk F, Duru ME, Topçu G. Antioxidant activity of stem and root extracts of Rhubarb (Rheum ribes): An edible medicinal plant. Food Chemistry. 2007; 103(2): 623-30.
101. Burits M, Bucar F. Antioxidant activity of Nigella sativa essential oil. Phytotherapy Research. 2000; 14(5): 323-8.
102. Kumar MP. Comparative evaluation of anti gastric ulcer activity of root, stem and leaves of Thalictrum foliolosum DC in rats. VRI Phytomedicine. 2013; 1(1): 3-7.
103. Nabavi SF, Habtemariam S, Ahmed T, Sureda A, Daglia M, Sobarzo-Sánchez E, et al. Polyphenolic Composition of Crataegus monogyna Jacq.: From Chemistry to Medical Applications. Nutrients. 2015; 7(9): 7708-28.
104. Deineka V, Gabruk N, Deineka L, Manokhina L. Triglyceride composition of oil from stones of nine Rosaceae plants. Chemistry of natural compounds. 2002; 38(5): 410-2.
105. Yildirim A, OKTAY M, BİLALOĞLU V. The antioxidant activity of the leaves of Cydonia vulgaris. Turkish Journal of Medical Sciences. 2001; 31(1): 23-7.
106. Hagen SF, Borge GIA, Bengtsson GB, Bilger W, Berge A, Haffner K, et al. Phenolic contents and other health and sensory related properties of apple fruit (Malus domestica Borkh., cv. Aroma): Effect of postharvest UV-B irradiation. Postharvest Biology and Technology. 2007; 45(1): 1-10.
107. Shahaboddin M-E, Pouramir M, Moghadamnia A-A, Parsian H, Lakzaei M, Mir H. Pyrus biossieriana Buhse leaf extract: An antioxidant, antihyperglycaemic and antihyperlipidemic agent. Food chemistry. 2011; 126(4): 1730-3.
108. Wang Y, Chen X, Zhang Y, Chen X. Antioxidant activities and major anthocyanins of myrobalan plum (Prunus cerasifera Ehrh.). Journal of food science. 2012; 77(4): C388-C93.
109. Gharabaghi PM, Tabatabei F, Fard SA, Sayyah-Melli M, Del Azar EOA, Khoei SA, et al. Evaluation of the effect of preemptive administration of Rosa damascena extract on post-operative pain in elective cesarean sections. African Journal of Pharmacy and Pharmacology. 2011; 5(16): 1950-5.
110. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation. Journal of general internal medicine. 2008; 23(6): 854-9.
111. Lua PL, Zakaria NS. A brief review of current scientific evidence involving aromatherapy use for nausea and vomiting. The Journal of Alternative and Complementary Medicine. 2012; 18(6): 534-40.
112. Arias BA, Ramón-Laca L. Pharmacological properties of citrus and their ancient and medieval uses in the Mediterranean region. Journal of Ethnopharmacology. 2005; 97(1): 89-95.
113. Oben J, Enonchong E, Kothari S, Chambliss W, Garrison R, Dolnick D. Phellodendron and Citrus

extracts benefit joint health in osteoarthritis patients: a pilot, double-blind, placebo-controlled study. Nutrition journal. 2009; 8(1): 1.
114. Jagetia GC, Venkatesh P, Baliga MS. Fruit extract of Aegle marmelos protects mice against radiation-induced lethality. Integrative cancer therapies. 2004; 3(4): 323-32.
115. Arulmozhi D, Veeranjaneyulu A, Bodhankar S, Arora S. Investigations of Sapindus trifoliatus in dopaminergic and serotonergic systems: Putative antimigraine mechanisms. Indian journal of pharmacology. 2005; 37(2): 120.
116. Coon JST, Ernst E. Herbs for serum cholesterol reduction: a systematic review.(Original Research). Journal of Family Practice. 2003; 52(6): 468-79.
117. Hashim YZH-Y, Kerr PG, Abbas P, Salleh HM. Aquilaria spp.(agarwood) as source of health beneficial compounds: A review of traditional use, phytochemistry and pharmacology. Journal of Ethnopharmacology. 2016; 189: 331-60.
118. Sharma M, Jain U, Patel A, Gupta N. A comprehensive pharmacognostic report on valerian. International journal of pharmaceutical sciences and research. 2010; 1(7): 6-40.
119. Chauhan RS, Tiwari D, Bisht A, Shukla A. Ex situ conservation of medicinal and aromatic plants in Bharsar, Uttarakhand, India. Medicinal Plants-International Journal of Phytomedicines and Related Industries. 2014; 6(4): 282-92.
120. Jayaprakasha G, Singh R, Sakariah K. Antioxidant activity of grape seed (Vitis vinifera) extracts on peroxidation models in vitro. Food chemistry. 2001; 73(3): 285-90.
121. Abascal K, Yarnell E. Clinical uses of Zingiber officinale (ginger). Alternative and Complimentary Therapies. 2009; 15(5): 231-7.
122. Giacosa A, Morazzoni P, Bombardelli E, Riva A, Bianchi PG, Rondanelli M. Can nausea and vomiting be treated with ginger extract. Eur Rev Med Pharmacol Sci. 2015; 19(7): 1291-6.
123. Chase MW, Morton CM, Kallunki JA. Phylogenetic relationships of Rutaceae: a cladistic analysis of the subfamilies using evidence from RBC and ATP sequence variation. American Journal of Botany. 1999; 86(8): 1191-9.
124. Nannapaneni R, Chalova VI, Crandall PG, Ricke SC, Johnson MG, O'Bryan CA. Campylobacter and Arcobacter species sensitivity to commercial orange oil fractions. International journal of food microbiology. 2009; 129(1): 43-9.
125. Javed S, Javaid A, Nawaz S, Saeed M, Mahmood Z, Siddiqui S, et al. Phytochemistry, GC-MS Analysis, Antioxidant and Antimicrobial Potential of Essential Oil From Five Citrus Species. Journal of Agricultural Science. 2014; 6(3): 201.
126. Ling Y, Yang D, Shao W. Understanding vomiting from the perspective of traditional Chinese medicine. Annals of palliative medicine. 2012; 1(2): 143-60.
127. Mokhber-Dezfuli N, Saeidnia S, Gohari AR, Kurepaz-Mahmoodabadi M. Phytochemistry and pharmacology of berberis species. Pharmacognosy reviews. 2014; 8(15): 8.
128. Akbulut M, ÇALIŞIR S, MARAKOĞLU T, COklar H. Some Physicomechanical and nutritional properties of barberry (Berberis vulgaris L.) fruits. Journal of food process engineering. 2009; 32(4): 497-511.
129. Menashian L, Flam M, Douglas-Paxton D, Raymond J. Improved food intake and reduced nausea and vomiting in patients given a restricted diet while receiving cisplatin chemotherapy. Journal of the American Dietetic Association. 1992; 92(1): 58-61.
130. Okunrobo LO, Imafidon KE, Alabi AA. Phytochemical, proximate and metal content analysis of the leaves of Psidium guajava Linn (Myrtaceae). International Journal of Health Research. 2010; 3(4): 217-21.
131. Yadegarinia D, Gachkar L, Rezaei MB, Taghizadeh M, Astaneh SA, Rasooli I. Biochemical activities of Iranian Mentha piperita L. and Myrtus communis L. essential oils. Phytochemistry. 2006; 67(12): 1249-55.
132. Tayarani-Najaran Z, Talasaz-Firoozi E, Nasiri R, Jalali N, Hassanzadeh M. Antiemetic activity of volatile oil from Mentha spicata and Mentha× piperita in chemotherapy-induced nausea and vomiting. ecancermedicalscience. 2013; 7: 290.
133. Samarth R, Kumar A. Radioprotection of Swiss albino mice by plant extract Mentha piperita (Linn.). Journal of radiation research. 2003; 44(2): 101-9.
134. Hernán G, Varela BG, Fortunato RH, Wagner ML. Pharmacobotany of Two Valeriana Species (Valerianaceae) of Argentinian Patagonia Known as "Ñancolahuen". Lat Am J Pharm. 2014; 33(6): 891-6.
135. Patočka J, Jakl J. Biomedically relevant chemical constituents of Valeriana officinalis. Journal of Applied Biomedicine. 2010; 8(1): 11-8.
136. Barton DL, Atherton PJ, Bauer BA, Moore Jr DF, Mattar BI, LaVasseur BI, et al. The use of valeriana officinalis (valerian) in improving sleep in patients who are undergoing treatment for cancer: a phase III randomized, placebo-controlled, double-blind study: NCCTG Trial, N01C5. The journal of supportive oncology. 2011; 9(1): 24.
137. Ryan JL, Heckler CE, Roscoe JA, Dakhil SR, Kirshner J, Flynn PJ, et al. Ginger (Zingiber officinale) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. Supportive care in cancer. 2012; 20(7): 1479-89.
138. Adib-Hajbaghery M, Hosseini FS. Investigating the effects of inhaling ginger essence on post-nephrectomy nausea and vomiting. Complementary therapies in medicine. 2015; 23(6): 827-31.

Global Journals Guidelines Handbook 2018

www.GlobalJournals.org

FELLOWS

FELLOW OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (FARSM)

Global Journals Incorporate (USA) is accredited by Open Association of Research Society (OARS), U.S.A and in turn, awards "FARSM" title to individuals.The 'FARSM' title is accorded to a selected professional after the approval of the Editor-in-Chief/Editorial Board Members/Dean.

- The "FARSM" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall,Ph.D., FARSS or William Walldroff, M.S., FARSM.

FARSM accrediting is an honor. It authenticates your research activities. After recognition as FARSM, you can add 'FARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, and Visiting Card etc.

The following benefits can be availed by you only for next three years from the date of certification:

FARSM designated members are entitled to avail a 40% discount while publishing their research papers (of a single author) with Global Journals Incorporation (USA), if the same is accepted by Editorial Board/Peer Reviewers. If you are a main author or co-author in case of multiple authors, you will be entitled to avail discount of 10%.

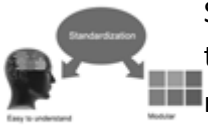
Once FARSM title is accorded, the Fellow is authorized to organize a symposium/seminar/conference on behalf of Global Journal Incorporation (USA). The Fellow can also participate in conference/seminar/symposium organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent.

You may join as member of the Editorial Board of Global Journals Incorporation (USA) after successful completion of three years as Fellow and as Peer Reviewer. In addition, it is also desirable that you should organize seminar/symposium/conference at least once.

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

The FARSM can go through standards of OARS. You can also play vital role if you have any suggestions so that proper amendment can take place to improve the same for the benefit of entire research community.

As FARSM, you will be given a renowned, secure and free professional email addres with 100 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.



The FARSM will be eligible for a free application of standardization of their researches. Standardization of research will be subject to acceptability within stipulated norms as the next step after publishing in a journal. We shall depute a team of specialized research professionals who will render their services for elevating your researches to next higher level, which is worldwide open standardization.

The FARSM member can apply for grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A. Once you are designated as FARSM, you may send us a scanned copy of all of you credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria. After certification of all your credentials by OARS, they will be published on your Fellow Profile link on website https://associationofresearch.org which will be helpful to upgrade the dignity.

The FARSM members can avail the benefits of free research podcasting in Global Research Radio with their research documents. After publishing the work, (including published elsewhere worldwide with proper authorization) you can upload your research paper with your recorded voice or you can utilize chargeable services of our professional RJs to record your paper in their voice on request.

The FARSM member also entitled to get the benefits of free research podcasting of their research documents through video clips. We can also streamline your conference videos and display your slides/ online slides and online research video clips at reasonable charges, on request.

The FARSM is eligible to earn from sales proceeds of his/her researches/reference/review Books or literature, while publishing with Global Journals. The FARSS can decide whether he/she would like to publish his/her research in a closed manner. In this case, whenever readers purchase that individual research paper for reading, maximum 60% of its profit earned as royalty by Global Journals, will be credited to his/her bank account. The entire entitled amount will be credited to his/her bank account exceeding limit of minimum fixed balance. There is no minimum time limit for collection. The FARSM member can decide its price and we can help in making the right decision.

The FARSM member is eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get remuneration of 15% of author fees, taken from the author of a respective paper. After reviewing 5 or more papers you can request to transfer the amount to your bank account.

MEMBER OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (MARSM)

The ' MARSM ' title is accorded to a selected professional after the approval of the Editor-in-Chief / Editorial Board Members/Dean.

The "MARSM" is a dignified ornament which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., MARSM or William Walldroff, M.S., MARSM.

MARSM accrediting is an honor. It authenticates your research activities. Afterbecoming MARSM,you can add 'MARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, Visiting Card and Name Plate etc.

The following benefitscan be availed by you only for next three years from the date of certification.

MARSM designated members are entitled to avail a 25% discount while publishing their research papers (of a single author) in Global Journals Inc., if the same is accepted by our Editorial Board and Peer Reviewers. If you are a main author or co-author of a group of authors, you will get discount of 10%.

As MARSM, you willbe given a renowned, secure and free professional email address with 30 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

The MARSM member can apply for approval, grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A.

Once you are designated as MARSM, you may send us a scanned copy of all of your credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria.

It is mandatory to read all terms and conditions carefully.

AUXILIARY MEMBERSHIPS

Institutional Fellow of Open Association of Research Society (USA) - OARS (USA)

Global Journals Incorporation (USA) is accredited by Open Association of Research Society, U.S.A (OARS) and in turn, affiliates research institutions as "Institutional Fellow of Open Association of Research Society" (IFOARS).

The "FARSC" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., FARSC or William Walldroff, M.S., FARSC.

The IFOARS institution is entitled to form a Board comprised of one Chairperson and three to five board members preferably from different streams. The Board will be recognized as "Institutional Board of Open Association of Research Society"-(IBOARS).

The Institute will be entitled to following benefits:

The IBOARS can initially review research papers of their institute and recommend them to publish with respective journal of Global Journals. It can also review the papers of other institutions after obtaining our consent. The second review will be done by peer reviewer of Global Journals Incorporation (USA) The Board is at liberty to appoint a peer reviewer with the approval of chairperson after consulting us.

The author fees of such paper may be waived off up to 40%.

The Global Journals Incorporation (USA) at its discretion can also refer double blind peer reviewed paper at their end to the board for the verification and to get recommendation for final stage of acceptance of publication.

The IBOARS can organize symposium/seminar/conference in their country on behalf of Global Journals Incorporation (USA)-OARS (USA). The terms and conditions can be discussed separately.

The Board can also play vital role by exploring and giving valuable suggestions regarding the Standards of "Open Association of Research Society, U.S.A (OARS)" so that proper amendment can take place for the benefit of entire research community. We shall provide details of particular standard only on receipt of request from the Board.

The board members can also join us as Individual Fellow with 40% discount on total fees applicable to Individual Fellow. They will be entitled to avail all the benefits as declared. Please visit Individual Fellow-sub menu of GlobalJournals.org to have more relevant details.

We shall provide you intimation regarding launching of e-version of journal of your stream time to time. This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

After nomination of your institution as "Institutional Fellow" and constantly functioning successfully for one year, we can consider giving recognition to your institute to function as Regional/Zonal office on our behalf.
The board can also take up the additional allied activities for betterment after our consultation.

The following entitlements are applicable to individual Fellows:

Open Association of Research Society, U.S.A (OARS) By-laws states that an individual Fellow may use the designations as applicable, or the corresponding initials. The Credentials of individual Fellow and Associate designations signify that the individual has gained knowledge of the fundamental concepts. One is magnanimous and proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice.

Open Association of Research Society (US)/ Global Journals Incorporation (USA), as described in Corporate Statements, are educational, research publishing and professional membership organizations. Achieving our individual Fellow or Associate status is based mainly on meeting stated educational research requirements.

Disbursement of 40% Royalty earned through Global Journals : Researcher = 50%, Peer Reviewer = 37.50%, Institution = 12.50% E.g. Out of 40%, the 20% benefit should be passed on to researcher, 15 % benefit towards remuneration should be given to a reviewer and remaining 5% is to be retained by the institution.

We shall provide print version of 12 issues of any three journals [as per your requirement] out of our 38 journals worth $ 2376 USD.

Other:

The individual Fellow and Associate designations accredited by Open Association of Research Society (US) credentials signify guarantees following achievements:

- The professional accredited with Fellow honor, is entitled to various benefits viz. name, fame, honor, regular flow of income, secured bright future, social status etc.

- In addition to above, if one is single author, then entitled to 40% discount on publishing research paper and can get 10%discount if one is co-author or main author among group of authors.
- The Fellow can organize symposium/seminar/conference on behalf of Global Journals Incorporation (USA) and he/she can also attend the same organized by other institutes on behalf of Global Journals.
- The Fellow can become member of Editorial Board Member after completing 3yrs.
- The Fellow can earn 60% of sales proceeds from the sale of reference/review books/literature/publishing of research paper.
- Fellow can also join as paid peer reviewer and earn 15% remuneration of author charges and can also get an opportunity to join as member of the Editorial Board of Global Journals Incorporation (USA)
- • This individual has learned the basic methods of applying those concepts and techniques to common challenging situations. This individual has further demonstrated an in–depth understanding of the application of suitable techniques to a particular area of research practice.

Note :

"

- In future, if the board feels the necessity to change any board member, the same can be done with the consent of the chairperson along with anyone board member without our approval.
- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

During submission of the manuscript, the author is confirming an exclusive license agreement with Global Journals which gives Global Journals the authority to reproduce, reuse, and republish authors' research. We also believe in flexible copyright terms where copyright may remain with authors/employers/institutions as well. Contact your editor after acceptance to choose your copyright policy. You may follow this form for copyright transfers.

Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

save our planet

Global Journal of Medical Research

Visit us on the Web at www.GlobalJournals.org | www.MedicalResearchJournal.org
or email us at helpdesk@globaljournals.org

ISSN 9755896