ISSN 0974-5319

IJCP

International Journal of Community Pharmacy

The Official Publication of ACPI

www.acpisouth.in/ijcp-official-journal

Vol. 5 Issue No. 3 (Pages: 67) July - Sept. 2024

ISSN-0974-5319

Volume 5 **Issue 3**

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EDITORIAL OFFICE

INTERNATIONAL JOURNAL OF COMMUNITY PHARMACY
The Official Publication of Association of Community Pharmacists of India [ACPI]
Secretariat & Communication Address
Sarada Vilas College of Pharmacy
Krishnamurthy Puram, Mysuru – 570004, Karnataka
Ph: 0821-4262415

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Editorial

Embracing Change and Advancing Pharmacy Care

Hanumanthachar Joshi
Editor in Chief
International Journal of Community Pharmacy

In the dynamic landscape of healthcare, the role of pharmacists continues to evolve, offering new opportunities and challenges alike. As we navigate through these transformative times, it becomes increasingly clear that the future of pharmacy care hinges on our ability to adapt, innovate, and collaborate. Pharmacists are no longer just dispensers of medications; they are integral members of the healthcare team, playing crucial roles in patient education, chronic disease management, and preventive care. The COVID-19 pandemic underscored their importance, highlighting their frontline contributions in vaccination efforts, patient counselling, and ensuring continuity of care. Technological advancements are reshaping pharmacy practice, from automated dispensing systems to tele pharmacy services. These innovations not only enhance efficiency but also expand access to pharmaceutical expertise in underserved communities. Embracing digital solutions is not merely an option but a necessity in today's interconnected world.

Moreover, the landscape of healthcare policy and regulation is constantly shifting. As advocates for patient welfare, pharmacists must stay informed and actively engage in shaping policies that affect pharmacy practice. By fostering strong relationships with policymakers and healthcare stakeholders, we can amplify our collective voice and advocate for changes that benefit both patients and practitioners. Education remains fundamental to our profession's growth. Continuous learning equips pharmacists with the knowledge and skills needed to deliver evidence-based care and stay abreast of emerging therapies. Lifelong learning isn't just a professional obligation but a commitment to excellence and patient safety.

In this issue of International Journal of Community Pharmacy (IJCP), we explore these themes and more. From innovative pharmacy practices to the latest advancements in pharmaceutical sciences, each article and feature is crafted to inspire, inform, and empower our readers. As we look ahead, let us embrace change with optimism and determination. Together, let's harness the power of collaboration and innovation to elevate pharmacy care to new heights. By doing so, we fulfill our mission to improve patient outcomes and uphold the highest standards of healthcare excellence.

Invited Editorial

Antibiotic-Smart Hospitals and the fight against Antimicrobial Resistance: Lessons learned from the Kerala Model

Tanmayee Joshi, MS[1], Isha Patel, PhD[2*]

[1] C. U. Shah College of Pharmacy, SNDT Women's University, Maharashtra, India

[2] Prowess LLC, Virginia, USA

*_Corresponding Author:_ Isha Patel PhD

Principal Research Scientist, Prowess LLC, Charlottesville, VA 22903, United States. Email: isha@umich.edu

A Family Health Centre (FHC) located in Kakkodi in the Kozhikode district was declared as India's first antibiotic- smart hospital (ASH) by the Kerala Health Department in November 2023. Similarly, another FHC at Ozhalapathy, on the border of Tamil Nadu and Kerala was declared as a second antibiotic smart hospital in January 2024. As per the World Health Organization, antimicrobial resistance (AMR) has contributed to nearly 4.95 million deaths globally. [1] In addition to death and disability, AMR poses significant economic costs. The World Bank estimates that AMR could amount to 1 trillion dollars in additional healthcare costs by 2050, and 1 trillion dollars to 3.4 trillion dollars in gross domestic product losses per year by 2030. [2]

India carries one of the largest burdens of drug-resistant pathogens worldwide. While exact estimates of the distribution of the population burdened by AMR in India is not available, neonates and elderly are thought to be among the ones majorly affected. Two million deaths are projected to occur in India due to AMR by the year 2050. [3] The Indian government set up the National Task Force on AMR Containment in 2010 and the National Action Plan on AMR came into existence in 2017. In 2018, Kerala was the first state in India to set up the Kerala Antimicrobial Resistance Strategic Action Plan (KARSAP). The KARSAP model consisted of increasing public awareness among the general public about antibiotic abuse, which was carried out through usage of social media, organization of 'awareness week' programs in schools and colleges, integration of educational resources about AMR in school curriculum, and conducting training programs for pharmacists, nurses and support staff. The model also included standardization and upgradation of laboratories at the district and state level for detection of AMR. Surveillance of AMR associated with six species, namely *E. coli, Klebsiella spp., Acinetobacter spp., Pseudomonas aeruginosa, Staphylococcus aureus* and *Enterococcus spp.* were also done. Infection control and prevention of infections were strengthened as well by improving sterilization and disinfection in health centers, improving hand hygiene, and reducing sources of contamination. [4] For the first time in India, district and block-level AMR committees were established in Kerala which were applicable to agriculture and animal husbandry departments. [5]

In order to create ASHs in Kerala, efforts were made at various levels. These hospitals adopted AWaRe classification of antibiotics as recommended by WHO. The AWaRe classification categorizes antibiotics into three groups: access, watch and reserve. The 'Access' category consists of first-choice antibiotics that are typically narrow-spectrum and have less potential for resistance. The examples in this category include amoxicillin, cefalexin, chloramphenicol, and nitrofurantoin. These antibiotics are used in the first- and second-line treatment of infections. The 'Watch' category has broader-spectrum antibiotics with a higher potential of developing resistance such as fluoroquinolones and macrolides. Lastly, the 'Reserve' or last-resort antibiotics are used for multidrug-resistant infections. [6]

Apart from adopting the AWaRe classification, some more objectives were needed to be achieved in order to become an ASH. These objectives included constituting a committee at the hospital level and training of all healthcare workers in infection control and antimicrobial stewardship, alongwith conducting educational programs for general public every fortnight. Also, displaying AWaRe classification of antibiotics in prescribing areas and posters about AMR in local language (Malayalam) in all hospitals.

Prescription audits needed to be conducted in each quarter to evaluate whether the pharmacy dispensed antibiotics that were utilized, were in accordance with the AWaRe classification. It was necessary to ensure that more than ninety-five per cent antibiotic prescriptions in outpatient departments were from the access category. The National Quality Assurance Standards (NQAS) program recognizes good performing public health facilities. Its certification is an indication of the high credibility of such facilities in the community. It was necessary for the participating hospitals to already possess the NQAS certification or they had to plan to obtain one within the next year. The PROUD program (Programme on Removal of Unused Drugs) was jointly launched on a pilot basis by the State Drugs Control Department and All Kerala Chemists and Druggists' Association (AKCDA) to facilitate safe disposal of expired and unused antibiotics. [7,8]

Currently, India has three large operational AMR networks to collect AMR data from tertiary hospital settings. The National Center for Disease Control (NCDC) network is now the focal point for implementing the National Programme on Containment of Anti-Microbial Resistance and it collects data from a network of approximately sixty tertiary hospitals. The NCDC network uses WHONET, a standalone open-source windows-based software for data collection. The Hospital Acquired Infection (HAI) Surveillance Network is a collaborative effort by the All India Institute of Medical Sciences, Centers for Disease Control and Prevention and the Indian Council of Medical Research (ICMR) to strengthen the national capacity for surveillance of HAIs. The ICMR has established a network to collect data on AMR since 2013. This network uses an in-house web-based solution for collecting, managing, and analyzing its data, and is spread across thirty public tertiary care hospitals, some private hospitals and laboratories across India (e.g., SRL, Lal Path labs, etc.). [9] There are three of AMR data collection in India, namely i-AMRSS, that collects data, i-DIA that imports data from any other softwares, and the i-AMRIT that collects data from sites that do not use any surveillance tool. Over 0.4 million patient records have been collected so far by the one-stop AMR data repository. The data is available in the form of reports on the ICMR-AMR website (https://iamrsn.icmr.org.in/index.php/resources/amr-icmr-data). However, there is a restricted access to this collected data. [10]

Kerala was the first Indian state to form AMR block committees in all of its 191 health blocks. These committees consist of representatives from the departments of health, animal husbandry, fisheries, agriculture and environment. The campaign was implemented by AMR block committees and was monitored by district and state level committees. AMR awareness messages were prepared, collated and released in a flip book format in the regional language Malayalam for the public, farmers and students. Public engagement was routinely done through visual and print medium. Ninety five percent of the antibiotics prescribed at the hospitals were less prone to cause AMR since they were from the "Access" category recommended by the WHO. Furthermore, the Kerala government has also created a toll free number for reporting of pharmacies selling antibiotics without prescription and the health minister also intends to stop antibiotic sales without prescription in 2024. [7]

As per the National Centre for Disease Control's study comprising of twenty tertiary care hospitals in India conducted from November 2021 to April 2022, 71.9% of hospitalized patients are prescribed antibiotics, with 4.6% getting more than four antibiotics. Out of the prescribed antibiotics 57% were from Watch group and 38% belonged to Access group. Top antibiotics being prescribed across classes were Ceftraixone, Metronidazole and Amikacin. Only 8 out of 20 hospitals had antibiotic policy in place. [11] Based on the experiences of physicians working in the field, patients have many misconceptions about the proper intake of antibiotics and they prematurely stop taking them. It is also challenging to acquire data from primary and secondary care hospitals. Additionally, it is cumbersome to get private sector hospitals onboard since these hospitals are not part of the state surveillance network. [12]. India has grappled with AMR for decades and healthcare facilities face negative consequences because of AMR, leading to extended hospitalizations and untimely patient deaths. Nationwide establishment of ASHs similar to the ones implemented in the state of Kerala with good AMR data collection capabilities can aid our country in making the right strides towards managing AMR.

Research Article

A STUDY ON THE ASSESSMENT OF ETIOLOGICAL FACTORS OF LAPAROTOMY AND ITS DRUG UTILIZATION EVALUATION ALONG WITH CEFTRIAXONE RESISTANCE

Raghuveer [1] , Charan C S [2], Deekshha C [3], Malavika M V [4], Sanika Prasad K [5], Hanumanthachar Joshi [6], Bilal K V [7]

[1] Associate Professor Department of Surgery, Krishna Rajendra Hospital, MMC&RI, Mysuru.
[2] Associate Professor & Head Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru.
[3,4,5]5th Pharm D, Sarada Vilas college of pharmacy, Mysuru.
[6]Principal Sarada Vilas College of Pharmacy, Mysuru.
[7]Assistant Professor, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru.

ABSTRACT:

Aims and objectives: To study and analyse the prescription pattern of drugs post-laparotomy surgery, etiological factors of laparotomy surgery, and ceftriaxone resistance in the study population.

Materials and method: A prospective observational study of patients who underwent laparotomy surgery was carried out in the surgery department of K R Hospital, Mysuru for a period of six months. All relevant data of the enrolled patients was collected from various data sources and documented in suitably designed data collection forms to evaluate the causes of laparotomy and to understand the pattern and extent of medication by using Drug Utilization and Evaluation(DUE). The reports of blood cultures, wound cultures, or pus cultures of study participants will be evaluated to check for ceftriaxone resistance.

Results: Of 103 patients, 64.1% were male and 35.9% were female. Most patients were in the age group 31-40 years (29.1%). In this study, the most commonly prescribed class of drugs were Analgesics 21.9% (n=158), followed by Electrolytes 16.8% (n=121), Antibiotics 15.9% (n=103), PPI 14.3% (n=103) respectively. The most common etiological factors of laparotomy surgery were acute appendicitis 44.66% (n=46), acute intestinal obstruction 13.58% (n=14), and subacute intestinal obstruction 9.70% (n=10). Out of 103 patients, 12 patients underwent a culture sensitivity test and 58.33% (n=7) were resistant to ceftriaxone.

Conclusion: Gender and age of the study population had a significant association with the study and were majorly considered. The study observed that the strains of organisms that exhibit resistance to ceftriaxone are gram-negative bacteria *Escherichia coli* and gram-negative bacteria *Pseudomonas aeruginosa.* The most commonly used drugs were Analgesics, Electrolytes, Antibiotics, and PPI. Major etiological factors for performing laparotomy surgery were found to be acute appendicitis, acute intestinal obstruction, and sub-acute intestinal obstruction.

Keywords: Emergency Laparotomy, Exploratory Laparotomy, Appendicitis, Resistance, Ceftriaxone, Drug Utilization Evaluation.

INTRODUCTION:

Laparotomy is a surgical procedure performed by producing a significant abdominal incision to acquire access to the peritoneal cavity. Laparotomy is usually performed by making a sagittal, midline incision along the linea Alba. The main types of incision made include midline incision, transverse incision, pfannestial and rooftop incision. Major Causes of laparotomy surgery are acute intestinal obstruction, Intestinal perforation,Acute appendicitis, Peritonitis, and Perforated hollow viscous.

Types of Laparotomies considered for the study Emergency laparotomy, Exploratory laparotomy, Laparoscopic Appendectomy.

Preferable drugs used post laparotomy surgery are monotherapy or dual therapy of antibiotics and analgesics, along with PPI, Ondansetron, and vitamins.

Resistance development on Ceftriaxone:

The World Health Organization (WHO) asserts that "antibiotic resistance is one of the biggest threats to global health, food security, and development today". The frequency of resistant bacteria has increased as a result of the growing usage of antibiotics worldwide.

Each year, 4.95 million individuals worldwide pass away due to multidrug-resistant microorganisms (MDR).

Lack of knowledge of treatment and diagnosis has led to improper drug selection, dosage, resistance and ADRs.

To provide timely information on drug resistance, particularly for broad-spectrum medications like ceftriaxone, periodic drug resistance evaluation is required.

A patient post-operative is said to be resistant to the drug if the surgical site wound is not healed as expected by the treatment provided.

Resistance can be checked by culture and sensitivity tests.

Culture and Sensitivity Test:

For drug susceptibility tests clinical samples of urine, wound blood, body fluid, throat, cerebral fluid, ear discharge, and genital discharge are collected.

Drug Utilization Evaluation:

The World Health Organization (WHO) defines drug utilization evaluation (DUE) as a process that examines the medical, social, and financial effects of pharmaceutical marketing, distribution, prescribing, and use in society.

To assess prescription patterns, which includes keeping track of the prescriber's approach to drug prescription, to justify and reduce the expenses of medical care.

Drugs with a lot of side effects, high costs, or complex dosing schedules have frequently been the focus of DUEs. Drug utilization research is an effective method for obtaining cost-effective healthcare.

MATERIALS AND METHODS:

Study Site: Krishna Rajendra Hospital (KR), Mysore

Study Design: Prospective Observational study

Study Period: This study was conducted over a period of six months from March 2023 to August 2023

Study Population: The sample size of the study was 93 patients. Total number of cases collected for the study was 103.

The department selected for study: The study was conducted at the Department of Surgery.

Ethical approval for the study: The institutional ethics committee of Mysore Medical College And Research Institute approved this research.

Sources of data:

All the relevant and necessary data was collected from:

- Patient case records
- Inpatient case sheet
- Treatment chart
- Interview with the patients and caretaker
- Communicating with concerned clinicians and healthcare professionals
- Data collection form

Study tools:

The study procedure involves the use of some proformas for data collection, documentation, and analysis of the data. This includes the following:

- Patient Profile form
- Data Collection form

Inclusion Criteria:

- Patients above 18 years of age.
- Patients undergoing laparotomies such as emergency laparotomy, exploratory laparotomy, and laparoscopic appendicectomy.
- Patients receiving ceftriaxone and other managing drugs for laparotomy

Exclusion Criteria:

- Patients who are not willing to participate in the study.
- Pregnant and lactating women.

Statistical analysis:

Microsoft Office 2016 was used to conduct a statistical analysis and evaluate the data. To represent the outcomes, descriptive statistics like percentages and graphs were used.

RESULTS:

Demographic details of the study population:

103 participants from the surgery department who met our inclusion criteria and had been through a laparotomy (exploratory laparotomy, emergency laparotomy, laparoscopic appendectomy) were enrolled in the study.

Demographic data	Number of patients	Percentage
Age (in years)		
11-20	7	6.79%
21-30	20	19.4%
31-40	30	29.1%
41-50	9	8.73%
51-60	11	10.6%
61-70	12	11.6%
71-80	14	13.59%

Etiological Factors of Laparotomy Surgery:

Among 103 participants who had undergone laparotomy surgery (exploratory laparotomy, emergency laparotomy, laparoscopic appendectomy) were enrolled in the study. The etiological factors for laparotomy were such as acute appendicitis at 44.66% (n=46), acute intestinal obstruction at 13.58% (n=14), subacute intestinal obstruction at 9.70% (n=10), Hollow viscous perforation at 6.78% (n=7), Appendicular perforation 3.88% (n=4), generalized peritonitis 3.88% (n=4), large bowel obstruction 2.91% (n=3), jejunal perforation 1.94(n=2), generalized peritonitis with hollow viscous perforation 1.94(n=2), abdominal abscess 0.00009(n=1), appendicular abscess 0.00009(n=1), carcinoma head of pancreas 0.00009(n=1), generalized peritonitis 2º to blunt trauma to abdomen 0.00009(n=1), generalized peritonitis with intestinal perforation 0.00009(n=1), generalized peritonitis with jejunal perforation 0.00009(n=1), Inguinal hernia 0.00009(n=1), intestinal perforation 0.00009(n=1), jejunal perforation 0.00009(n=1), obstructed umbilical hernia 0.00009(n=1), obstruction of afferent loop 0.00009(n=1), PSAOS perforation 0.00009(n=1).

Gender		
Male	66	64.1%
Female	37	35.9%
Diet		
Vegetarian	15	14.5%
Mixed	88	85.4%
Marital status		
Single	35	33.9%
Married	68	66.01%
Smoking Status		
Smoker	41	39.80%
Non-Smoker	62	60.19%
Alcoholic Status		
Alcoholic	34	32.03%
Non-alcoholic	69	67.96%
Geographical Area		
Urban	29	28.15%
Rural	74	71.84%

Table 1: Sociodemographic profile of the study population

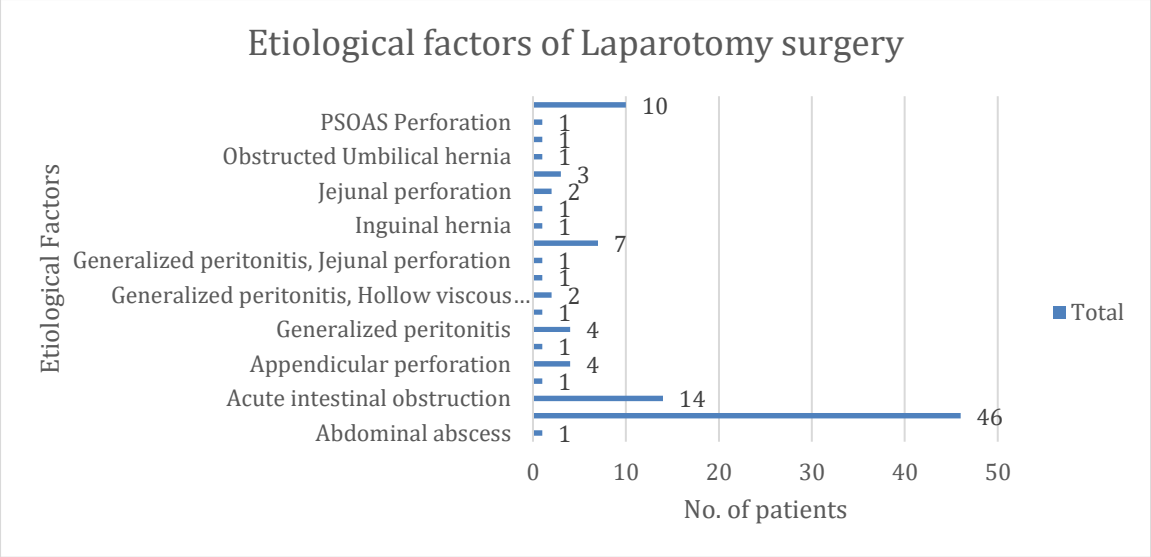

Figure 1: Distribution of patients based on etiological factors

Major Etiological Factors for Laparotomy Distribution according to Age group:

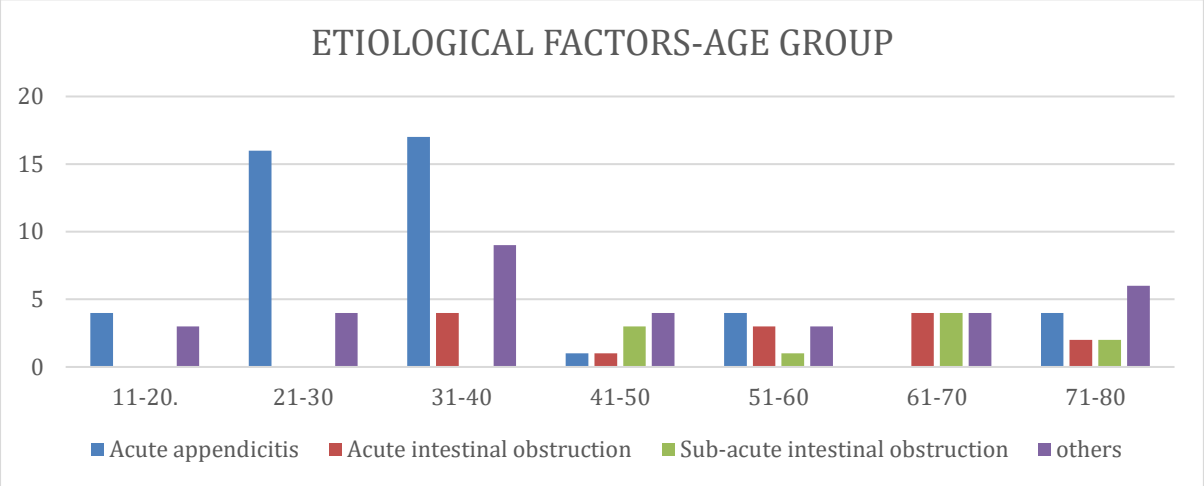

Figure 2: Distribution of patients on major etiological Factors based on Age Group

Major Etiological Factors for Laparotomy Distribution according to gender:

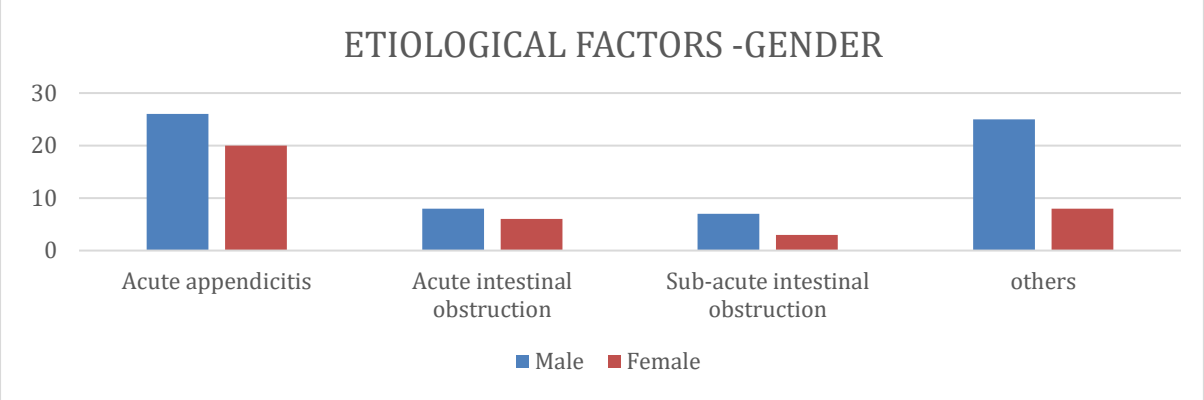

Figure 3: Distribution of patients on major Etiological Factors based on gender

Types of Laparotomy Surgery Conducted:

Among 103 patients, who had undergone three types of laparotomy surgery, exploratory laparotomy, emergency laparotomy, and laparoscopic appendectomy were enrolled in the study. The patients had done with Laparoscopic Appendectomy 49.51% (n=51), exploratory laparotomy 41.74% (n=43), and emergency laparotomy 8.73% (n=9).

Culture sensitivity test	No. of patients	Percentage
Wound culture conducted	12	11.6%
Wound culture not conducted	91	88.3%
Total	103	100%

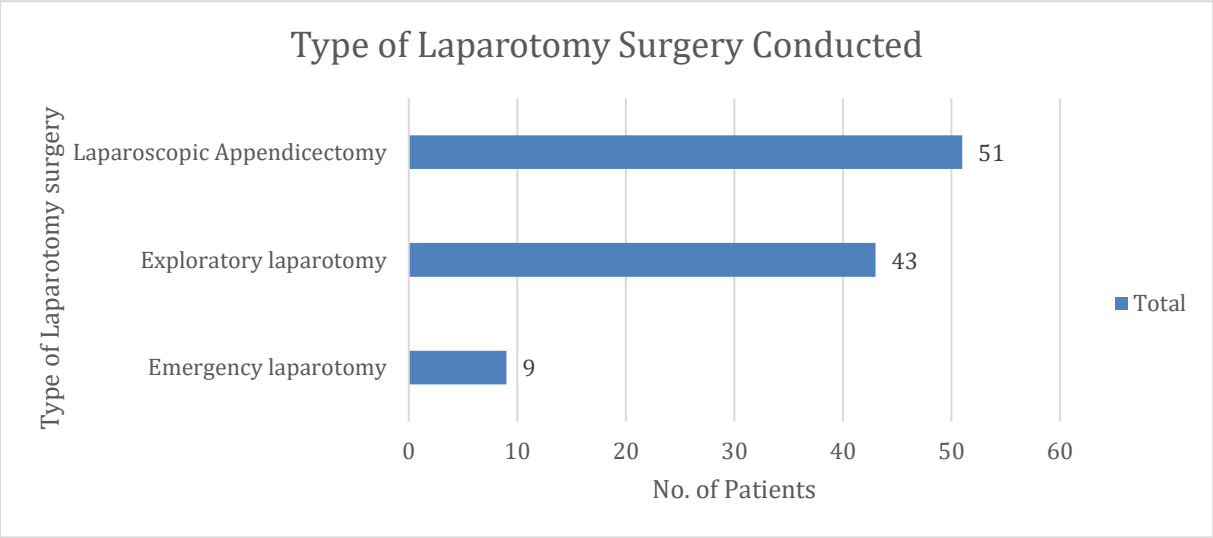

Figure 4: Distribution of patients based on Types of Laparotomy Surgery Conducted

Ceftriaxone treatment:

Ceftriaxone Treatment	No. of patients	Percentage
Prescribed	68	66.01%
Not Prescribed	35	33.9%
Total	103	100%

Table 2: Representation of the total Study population that received Ceftriaxone treatment

Among 103 patients, the antibiotic Ceftriaxone 1g IV was distributed; 66.01% (n=68) were prescribed Ceftriaxone and 33.9% (n=35) patients were not prescribed Ceftriaxone.

Resistance to Ceftriaxone:

From the result, among 103 patients, a culture sensitivity test was done only on 12 patients where 58.33% (n=7) of the population were resistant to the drug ceftriaxone and 5 were not detected as resistant to the drug Ceftriaxone.

Table 3: The study population underwent a Culture sensitivity test-detected to be resistant to Ceftriaxone count

Resistant to the drug Ceftriaxone based on Organism strains:

From the results of the Culture, sensitivity tests the patients who were resistant to the drug Ceftriaxone n=7, were divided based on the strains of organisms that exhibit Ceftriaxone resistance that is gram-negative bacteria *Escherichia coli* (n=4) and gram-negative bacteria *Pseudomonas aeruginosa* (n=3).

Organism	No. of Patients
Escherichia coli	4(57.14%)
Pseudomonas aeruginosa	3(42.8%)

Table 4: Resistant to the drug Ceftriaxone based on Organism strain count

Alternative Antibiotic therapy due to Ceftriaxone resistance development:

Due to the presence of bacterial strains showing resistance to the drug Ceftriaxone in 7 patients, to provide better antibiotic treatment post-surgery, alternative antibiotic drugs such as Piptaz (Piperacillin+ Tazobactam) along with Meropenem (n=5), and Piptaz (Piperacillin+ Tazobactam) along with Amikacin (n=2) were prescribed respectively.

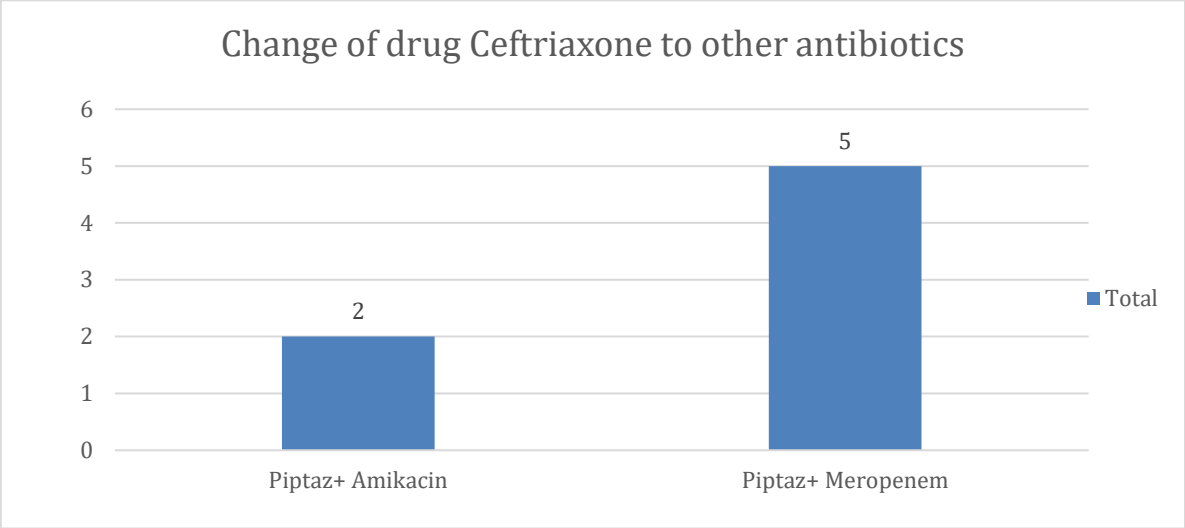

Figure 5: Representation of change of drug Ceftriaxone due to resistance development

Drug Utilisation Pattern

From the study population with a total number of 103 participants total of 720 drugs were prescribed the average number of drugs prescribed per prescription was found to be 6.99. In this study, the most commonly prescribed class of drugs were Analgesics (n=158, 21.9%), followed by Electrolytes (n=121, 16.8%), Antibiotics (n=115, 15.9%), PPI (n=103, 14.3%), Antiparasitic (n=84, 11.6%), Antiemetic (n=81, 11.2%), Vitamin (n=58, 8.05%) respectively.

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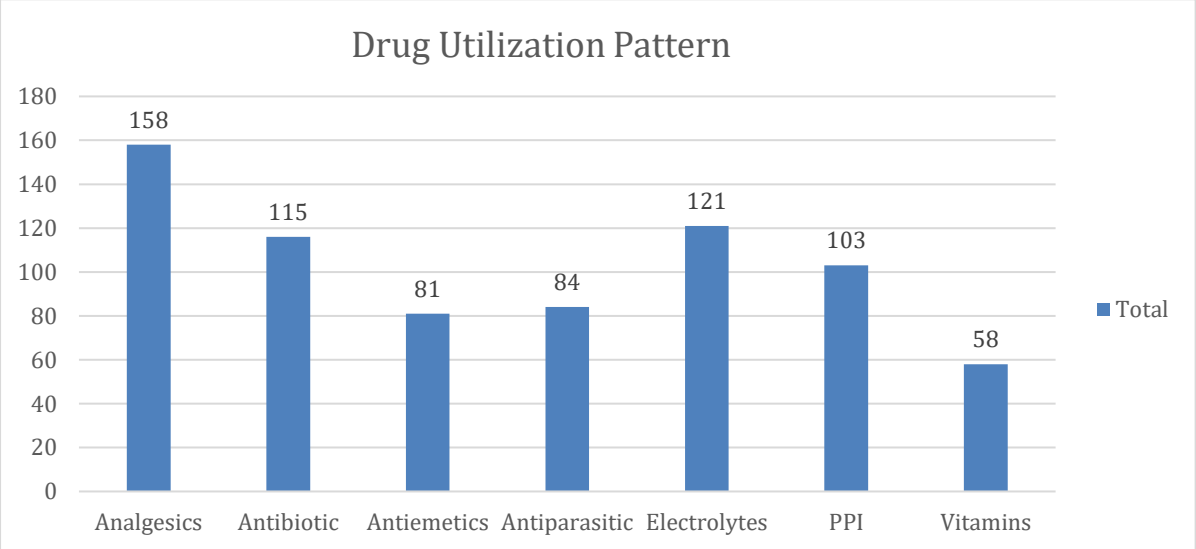

CONCLUSION:

The most commonly used drugs were Analgesics, Electrolytes, Antibiotics, and Proton pump inhibitors. Post laparotomy surgery, to avoid SSI (Surgical Site Infection) antibiotics were used and to relieve pain Analgesics were used. An average number of drugs prescribed per prescription showed polypharmacy. The percentage of drugs prescribed using the essential drug list was found to be moderate. The study was also conducted to observe ceftriaxone resistance in the study population. In this study, resistance to ceftriaxone was found to be less. Also, the study observed that the strains of organisms that exhibit resistance to ceftriaxone are gram-negative bacteria *Escherichia coli* and gram-negative bacteria *Pseudomonas aeruginosa*.

The study was also conducted to find the etiological factors for performing laparotomy surgery such as exploratory laparotomy, laparoscopic appendectomy, and emergency laparotomy. Majorly conducted laparotomy surgery was laparoscopic appendectomy. Major etiological factors for performing laparotomy surgery were found to be acute appendicitis, acute intestinal obstruction, and sub-acute intestinal obstruction.

The study gives an insight into rational drug use, especially of analgesics and antibiotics. Among observed cases, long-term use of opioid analgesics was seen. This can be rationalized by prescribing dual therapy of a low-dose opioid analgesic along with an NSAID.

Similarly, rational use of antibiotics can be implemented by prescribing fixed dose combinations.

ACKNOWLEDGMENT:

It is a genuine pleasure to express gratitude to our guide, **Dr. Charan C S**, Associate Professor and Head Department of Pharmacy Practice, Sarada Vilas College of Pharmacy.

We sincerely thank our co-guide 2, **Dr. Raghuveer**, Associate Professor Department of Surgery, Krishna Rajendra Hospital, MMC&RI, Mysuru.

We respect and thank **Dr. Hanumanthachar Joshi K**, Principal, Sarada Vilas College of Pharmacy.

We remember the support provided by our lecturer and co-guide 3, **Dr. Bilal K V**, Assistant Professor, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy.

Our special thanks to **Dr.Ravindra P Choudhary** for his moral support, suggestions, and guidance without which our work would not have been completed successfully.

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Research Article

A PROSPECTIVE OBSERVATIONAL STUDY ON MEASURING CLINICAL OUTCOMES OF ENOXAPARIN AND UNFRACTIONATED HEPARIN IN ACUTE CORONARY SYNDROME PATIENTS

Syed Anwar*[1], Anu Nagaraj[1], Jijo Joji[2], Venkatesh[3], Nikhil B[4], Charan C S[5], Hanumanthachar Joshi[6].

[1]Pharm D 5th year students, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

[2]Assistant Professor, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru.

[3]Professor and Head of the Department, Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru.

[4]Assistant Professor of Cardiology and Interventional Cardiologist, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru, Karnataka, India.

[5]Associate Professor and Head of the Department, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru.

[6]Principal, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

*Corresponding Author: Syed Anwar, Pharm D 5th year student, Sarada Vilas College of Pharmacy, Krishnamurthy Puram, Mysuru-570004, Karnataka, India.

Email: syedanwartnp786@gmail.com Contact: +917026367869

ABSTRACT:

Introduction: STEMI, NSTEMI and UA are included in Acute Coronary Syndrome. Anticoagulant medications such as enoxaparin and unfractionated heparin lower coagulation activity.

Objectives: To determine the health-related quality of life and pain in the patients treated with enoxaparin and unfractionated heparin.

Methods: A six-month cohort study was conducted at the Sri Jayadeva Institute of Cardiovascular Sciences and Research. Subject enrollment was based on the inclusion of patients above 18 years of age and the exclusion of pregnant and lactating women along with other severe comorbid conditions. Data, including patient demographics, medical history and medication records were collected. Pain and quality of life were assessed using various scales, documented in Microsoft Excel.

Results: A total of 160 patients who met the inclusion criteria were taken. 80 were administered with enoxaparin and 80 were administered with unfractionated heparin. The patients who received enoxaparin showed greater improvement in both the domains of SF-12 questionnaires and also in the visual analogue scale when compared to unfractionated heparin.

Conclusion: Clinical pharmacists play an important role in improving the health-related quality of life for patients with acute coronary syndrome by counseling the patients regarding their condition by educating them about the importance of taking medications regularly and monitoring the patients frequently.

Keywords: Acute coronary syndrome, Enoxaparin, Unfractionated heparin

INTRODUCTION:

The clinical presentation of acute coronary syndromes (ACS) is broad. It ranges from cardiac arrest and electrical or hemodynamic instability with cardiogenic shock (CS) due to ongoing ischemic complications such as severe mitral regurgitation, to patients who are currently not in pain at the time of presentation.

According to ECG alterations, ACS is divided into

1. ST-segment elevation myocardial infarction (STEMI)

2. Non-ST segment elevation myocardial infarction (NSTEMI)

3. Unstable angina

ANTICOAGULANTS:

Anticoagulants are also known as blood thinners. The primary goal of anticoagulant therapy in acute coronary syndrome is to prevent the formation and growth of blood clots.

1. ***Unfractionated heparin***

For many years, unfractionated heparin (UFH) has been the preferred antithrombotic medication.

UFH is administered intravenously. It binds to antithrombin III (AT III) and amplifies its inhibitory impact on Factor Xa. UFH needs to bind to AT and the enzyme to inhibit thrombin (Factor IIa). Heparin does not pass through the placenta or blood-brain barrier which makes it suitable for use as a pregnancy anticoagulant.

2. ***Enoxaparin***

Enoxaparin is a low molecular weight heparin (LMWH). Depolymerizing UFH chemically produces low molecular weight heparin.

There are several benefits over unfractionated heparin such as no platelet activation; better subcutaneous bioavailability (up to 90%); a decreased risk for Heparin-induced thrombocytopenia; and a longer half-life (i.e., twice a day dosing). These advantages make enoxaparin an attractive anticoagulant to be used in acute coronary syndrome management.

MATERIALS AND METHOD:

Study site: The study was conducted at Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru, Karnataka.

Study design: The study was a Prospective observational study.

Study population: We have considered 160 cases in a period of four months.

Study period: The study was carried out for a span of Six months.

Ethical approval: Ethical clearance for the study is obtained from the Institutional Ethical Committee,Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru, Karnataka.

Source of data: All the relevant and necessary data were obtained from

- Medical and medication records of the patient
- Interviewing patient and caretaker
- Communicating with concerned clinicians and healthcare professionals
- Telephonic contact or direct meeting with the patient if needed
- Various questionnaires
- Any other relevant source

STUDY CRITERIA:

Inclusion criteria

- Patients of either gender.
- Patients above 18 years of age.
- Patients diagnosed with ACS.
- Patients who are on enoxaparin medication.
- Patients who are on unfractionated heparin medication.

Exclusion criteria

- Incomplete case sheets.
- Incomplete medical and medication information.
- Pregnant or lactating women.
- Severe comorbid conditions.
- Patients who are not willing to participate in the study by giving informed consent.

STUDY PROCEDURE: The study involved the following steps:

1. Preparation of Informed Consent Form (ICF): An informed consent form was designed in English and the same was translated into the local language i.e., Kannada to acquire consent from patients who enrolled in the study. It is reviewed and approved by the Institutional Ethical Committee. The study was explained in detail to the patient and consent was obtained willingly after the patient had been informed of every aspect of the study. In illiterate patients, the study aspects were explained to the caretakers and consent from their caretakers was obtained.

2. Preparation of data collection form (DCF): A data collection form was suitably designed that included all relevant data of the enrolled patients including demographic details like name, age, gender, IP number, body weight, date of admission and clinical data such as diagnosis, stage of ACS, past medical history, past medication history, history of medication adherence, interventions made, co-morbidities, allergy status, the reason for admission, vitals, lab data, cardiac biomarkers, day

notes, 2D echo and doppler results, ECG and therapeutic data such as name of the drug prescribed, dose of the drug, its frequency, route of administration and duration of administration of the drug.

3. Patient enrollment: Patients who met the study criteria were enrolled in the study after obtaining informed consent. Patients were enrolled in intensive care units, general wards, deluxe wards and semi-deluxe wards
of the cardiology department. Based on their treatment i.e. those who are treated with enoxaparin and unfractionated heparin are enrolled.

4. Data collection: The in-charge authority of the cardiology department was informed and permission was obtained. Data of the patients matching the inclusion criteria were recorded. The patient consent form was given to the patient initially and all the aspects of the study were explained. Signature or thumb impression was obtained from the patients as well as caretakers in the case of illiterate patients. All relevant details of the enrolled patients including the demographics and treatment details were obtained from the patient's medical records and documented in the data collection form. The collected data were entered into the Excel sheet for analysis purposes. SF-12 questionnaire and visual analogue scale were also recorded.

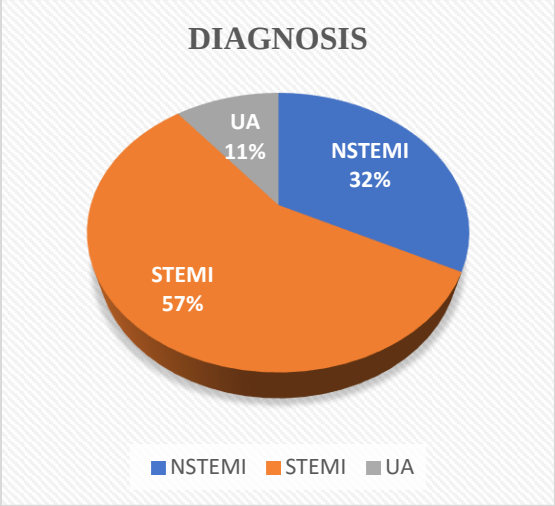
5. Statistical analysis: Data was collected, entered and assembled in Microsoft Office Excel 2021. The entered data was analyzed with the help of Microsoft Office Excel 2021 using descriptive statistical analysis to find out the frequency and percentage of age and gender distribution, quality of life and visual analogue scale. Suitable graphs, tables and charts were added.

RESULTS:

Among 160 patients enrolled in the study, 80 were administered with unfractionated heparin and the other 80 were administered with enoxaparin. 59% were male and 41% were female with the mean average of the population being 59.6 years.

GENDER	FREQUENCY	PERCENTAGE
MALE	94	59%
FEMALE	66	41%

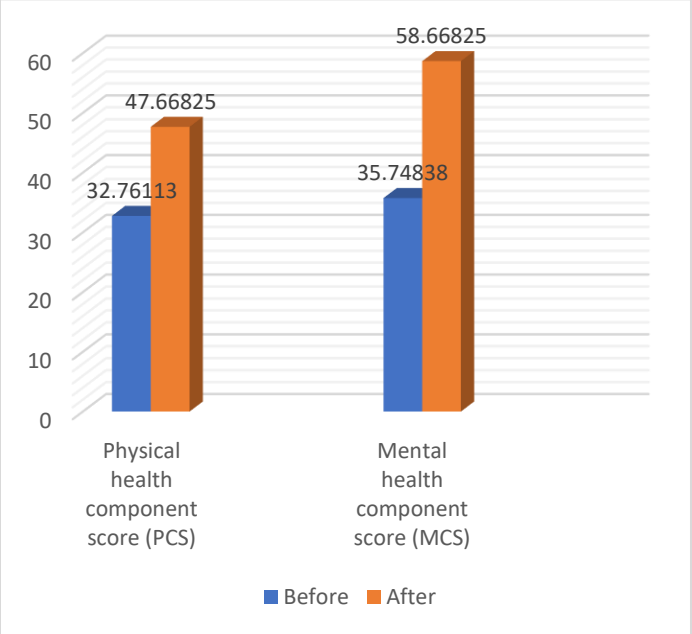
Diagnosis ST-elevated myocardial infarction (STEMI) was found in 91 patients, followed by non-ST-elevated myocardial infarction (NSTEMI) was found in 52 patients and Unstable angina (UA) was found in 17 patients.



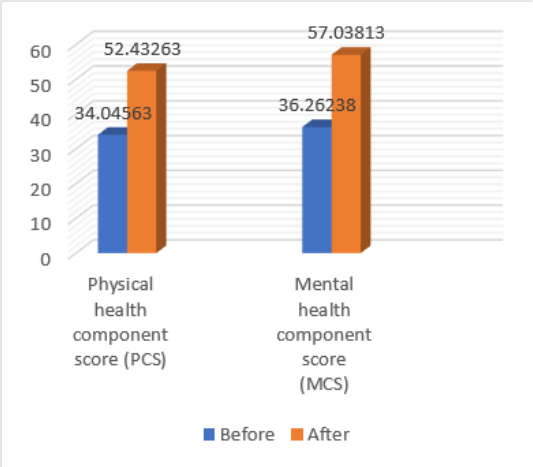
QUALITY OF LIFE

The quality of life was assessed twice using the SF-12 questionnaire, the patients were interviewed during the admission and then followed up after 1 month to calculate the improvement.

The mean quality of life in patients taking unfractionated heparin, the initial Physical health component score (PCS) and Mental health component score (MCS) were 32.76113 and 35.74838 respectively and the final Physical health component score (PCS) and Mental health component score (MCS) were 47.66825 and 58.66825 respectively.



The mean quality of life in patients taking enoxaparin, the initial Physical health component score (PCS) and Mental health component score (MCS) were 34.04563 and 36.26238 respectively and the final Physical health component score (PCS) and Mental health component score (MCS) were 52.43263 and 57.03813 respectively.



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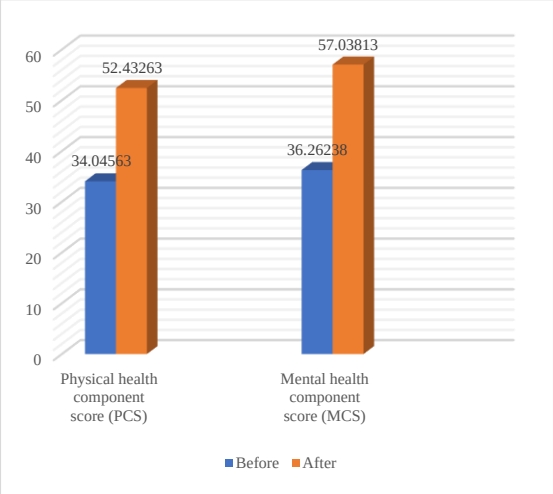
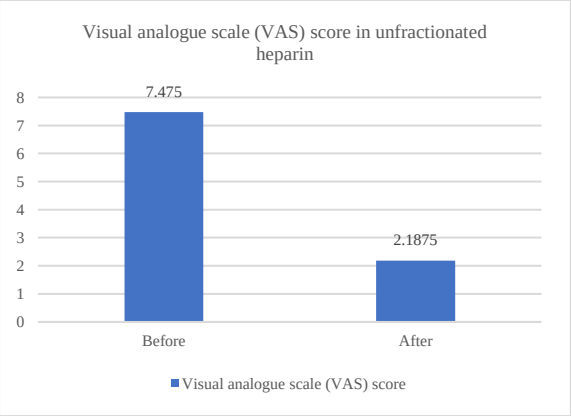
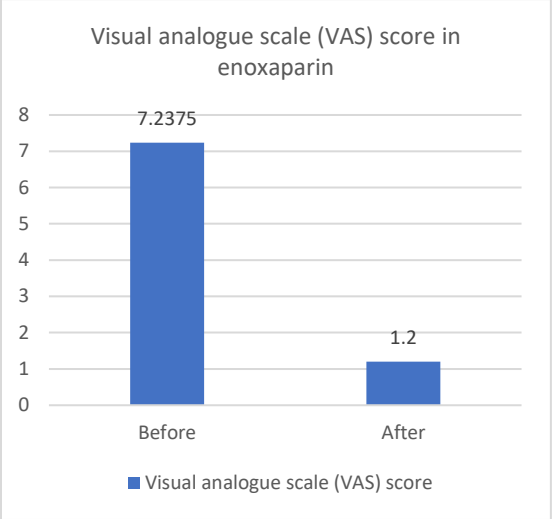


The mean visual analogue scale (VAS) in patients taking unfractionated heparin, the initial and final scores were 7.475 and 2.1875 respectively.



The mean visual analogue scale (VAS) in patients taking enoxaparin, the initial and final scores were 7.2375 and 1.2 respectively.



CONCLUSION:

The patients who received enoxaparin showed greater improvement in both the domains i.e., in the physical health component score (PCS) and mental health component score (MCS) of SF-12 questionnaire and also in the visual analogue scale when compared to unfractionated heparin.

Hence enoxaparin was found to be more effective in the aspect of overall HRQOL (health-related quality of life) and pain when compared to unfractionated heparin in acute coronary syndrome patients.

ACKNOWLEDGEMENT:

The authors are thankful to our Institutional guide **Mr. Venkatesh,** Professor and Head, Department of Pharmaceutics, SVCP, Mysuru. **Dr. Jijo Joji,** assistant professor, SVCP, Mysuru. **Dr. Charan C S**, Head of the Department, Department of Pharmacy Practice, SVCP, Mysuru and all the faculty members of the Department of Pharmacy Practice, SVCP, Mysuru. We also thank **Dr. Hanumanthachar Joshi,** Principal, Sarada Vilas College of Pharmacy, Mysuru and Special thanks to our clinical guide **Dr. Sadananda K S,** Professor and Medical Superintendent, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru. **Dr. Nikhil B,** assistant professor of cardiology and Interventional Cardiologist, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru.

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Review Article

A SYSTEMATIC REVIEW ON PHYTOCHEMICALS HAVING VASCULAR PROTECTIVE EFFECTS

Samruddhi Pisal, Siddhi Sawant

ABSTRACT:

Vascular endothelial dysfunction, characterized by imbalances in vasodilation and constriction, deficiency of nitric oxide bioavailability, and elevated reactive oxygen species, is a key factor in cardiovascular diseases like hypertension, atherosclerosis, and diabetes. Regular consumption of medicinal plants, fruits, and vegetables can promote vascular health and lower the risk of cardiovascular diseases. Phytochemical compounds found in these resources, such as curcumin have potential therapeutic agents for vascular dysfunction due to their antioxidative mechanisms. However, further human studies are needed to confirm these effects. Also, medicinal properties against CVDs of 4 widely used plants namely ginseng, ginkgo biloba, Ganoderma lucidum, gynostemma pentaphyllum are discussed in this review to provide recent information on their vascular protective mechanisms in vivo and in vitro. However, future human studies will be necessary to confirm the clinical effects of these vascular protective mechanisms. Finally, we reviewed and reported the results of the recent clinical trials and have been conducted using these medicinal herbs with special emphasis on their efficacy, safety, and toxicity. Marketed formulations and case studies regarding to vascular protective effect are also mentioned. Our study aimed to analyse and compare monthly costs along with cost variation between Ayurveda and Allopathy medicines used to treat 2 chronic disease conditions, viz. Atherosclerosis and Hypertension. The prices of Allopathic & Ayurvedic drugs mentioned in the treatment guidelines for these 2 conditions were obtained from different sources. In the case of Allopathic drugs, the %CVD ranged from 182%for DMARDs to 1184.39% for Corticosteroids. In the case of Anti-hypertensive medicines, too, the mean %CVD ranged from 84.21% for Rasaushadhi to 353.33% for Arishta, while %CVD ranged from 150.70% for ACE inhibitors to 269.85% for Calcium channel blockers for Ayurvedic and Allopathic medicines, respectively.

INTRODUCTION:

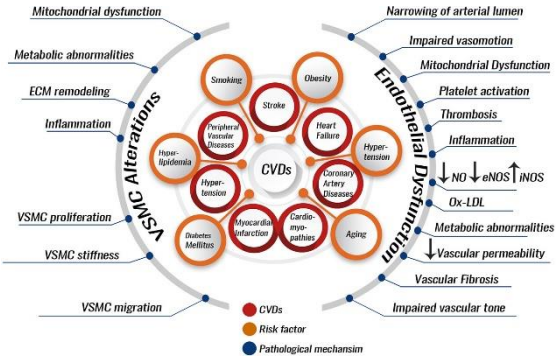
Low levels of nitric oxide gas in blood vessel walls cause endothelial disfunction, leading to coronary artery diseases, angina, chest pain, increased cardiovascular disease risk, atherosclerosis, and high blood pressure. Cardiovascular diseases (CVDs) are the leading cause of death worldwide. According to the World Health Organization (WHO), the almost 18 million deaths due to CVDs accounted for 32% of global deaths in 2019. This report also revealed that CVDs do not exclusively affect industrialized countries, as over three-quarters of CVD-related deaths occur in low- and middle-income countries. Older projections have already indicated that this number is expected to increase to over 23 million by 2030[1].

In addition to being the major cause of death worldwide, CVDs also lead to a great number of chronically ill patients, and as a consequence, to an immense socio-economic burden. Thus, there is an urgent global need for efficient CVD prevention. There are numerous established risk factors for the development and progression of CVDs.The aging process per se is a non-modifiable risk factor, as it cannot be reversed. On the contrary, other factors such as obesity, which, according to the WHO report on global health risks, is one of the major causes of ischemic heart disease, are modifiable, meaning that measures can be taken to change them and thereby reduce the risk for CVDs. Many natural substances have been used in traditional medicine in many regions of the world, often for thousands of years. In this review, we will highlight the impact of curcumin and some other phytocompounds on age-related cardiovascular dysfunction, adipose tissue, and obesity, as well as its protective effects in atherosclerosis and myocardial infarction. Cardiovascular diseases (CVDs), affecting over 17 million people annually, are the world's most common cause of death and a significant economic and health burden, accounting for 31% of annual global deaths. CVD, a condition characterized by vascular disfunction, can lead to heart failure, heart attacks, stroke, cardiomyopathies, dyslipidemias, and hypertension, causing organ damage. This

review critically assesses VEGF (vascular endothelial growth factor) therapy based on therapeutic angiogenesis and advances an alternative mechanism of vascular protection. Vascular protection involves VEGF-induced enhancement of endothelial functions, inhibiting vascular smooth muscle cell proliferation, enhancing endothelial cell survival, suppressing thrombosis, and anti-inflammatory effects. Investigation into vascular protection could help develop novel therapeutic approaches based on local VEGF gene delivery. This paper reviews phytocompounds from plants, vegetables, and fruits that offer anti-inflammatory and antioxidant properties, particularly in treating cardiovascular disorders. It also explores the mechanisms by which these compounds can improve vascular endothelial cell integrity, highlighting the potential benefits of herbal medicine over medications due to their low toxicity and clinical effectiveness. CVDs affect vessels and the heart, with atherosclerosis being a complex disease driven by low-grade inflammation. It begins with cholesterol deposition in vessel walls and chronic inflammatory reactions, leading to endothelial dysfunction in arteries prone to plaque development. Under homeostatic conditions, ROS production is counteracted by anti-oxidative systems, which are downregulated by CVD risk factors. As we age, our vascular and heart structures undergo significant changes, increasing the risk of cardiovascular events. These include endothelial dysfunction, aortic stiffening, elevated blood pressure, heart hypertrophy, and remodelling of myocardial microvasculature. [2, 3,8]

Risk factors for CVDs include hypertension, smoking, unhealthy diet, and endocrinopathies. These factors lead to pathological alterations, primarily due to endothelial dysfunction or VSMC alterations. These alterations increase the risk of atherosclerosis and hypertension, which are CVD risk factors and enhancers for other cardiovascular diseases. Vascular impairment is primarily caused by atherosclerosis, thrombosis, and high blood pressure, with common risk factors including smoking, unhealthy diet, diabetes, hyperlipidemia, and hypertension. Inflammation can impair the function of endothelial cells (ECs) in atherosclerosis, leading to the accumulation of oxidized LDL particles in the vessel wall intima.

Hypertension, a major risk factor for cardiovascular diseases (CVDs), is an independent predisposing factor for heart failure, coronary artery disease, stroke, retinopathy, nephropathy, and peripheral arterial diseases Strokes can impact cognitive and physical behaviors, potentially leading to dementia, paralysis, or even death. Vascular resistance is influenced by the sympathetic nervous system, rennin-angiotensin system, humoral factors, and local autoregulation. SNS and RAS primarily cause vasoconstriction and sodium retention through humoral mediators like endothelin, angiotensin II, catecholamines, and nitric oxide (NO), prostaglandins, and kinins. Endothelial dysfunction affects your endothelium. This thin layer of cells lines the inside of blood vessels. Dysfunction means the cells don't work the way they should. Instead of keeping blood vessels open (dilated), the cells cause your blood vessels to constrict or narrow. The condition is caused by vasospasm — a type of coronary artery disease. This means your coronary arteries become narrow even though there isn't a physical blockage. Endothelial dysfunction also increases the risk of coronary arterial disease from atherosclerosis. [2,3].

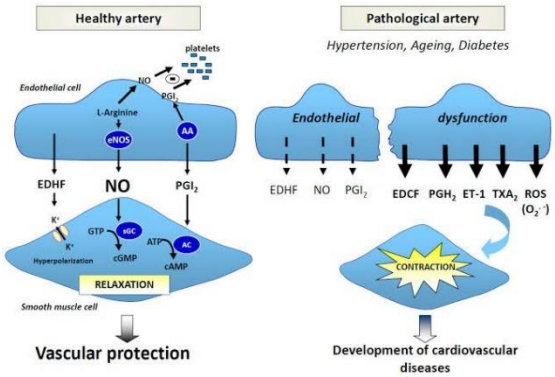


(Fig. 1.1) Pathological Processes Involved in the Development and Progression of CVDs [2]

PATHOPHYSIOLOGY:

Endothelial cells are crucial in maintaining the homeostasis of the cardiovascular system, regulating blood flow, vascular tone, angiogenesis, vascular permeability, leukocyte adhesion, and platelet aggregation. They form a semipermeable barrier that allows substances to pass through between the blood and the vascular wall. Endothelial cells secrete localized chemicals, such as nitric oxide (NO), prostacyclin, and endothelin, to control blood vessels and regulate blood flow. They also play a vital role in blood flow regulation, generating a prothrombotic and anti-fibrinolytic milieu in response to perturbations. Endothelial cells also regulate vascular tone, maintaining a balance between vasorelaxing and vaso-constricting factors in the blood. They also coordinate leukocyte trafficking during vascular injuries, facilitating the recruitment and migration of leukocytes to the subendothelial space. The development of vascular disease is dependent on the activation of vascular endothelial cells, which increase the expression of proinflammatory mediators, chemokines, and growth factors, leading to impaired vascular tone, endothelial-dependent vasodilation, and redox imbalance.

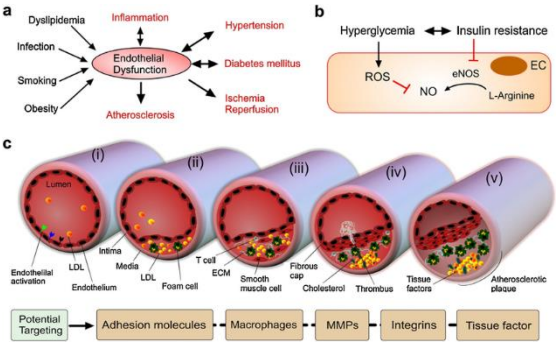
Endothelial dysfunction is a key factor in various human diseases, including PAD, cardiovascular diseases, stroke, chronic kidney failure, cancer, and infectious diseases. This coronary artery disease narrows your arteries, causing angina or chest pain. The condition increases the risk of cardiovascular disease, atherosclerosis and high blood pressure. Lifestyle changes and medications can treat it. [5,8]



(Fig. 2.1) Pathophysiology of Vascular Dysfunction

Causes

Endothelial dysfunction is a condition affecting the endothelium, a thin layer of cells that lines the inside of blood vessels. It causes blood vessels to constrict or narrow, leading to vasospasm, a type of coronary artery disease. This condition increases the risk of coronary artery disease from atherosclerosis. The endothelium controls fluids and electrolytes in the blood, helps clot blood when needed, keeps toxins out of tissues, and regulates tissue inflammation. Initially thought to be a barrier in blood vessels, endothelial dysfunction was recognized as an organ system in the late 1990s. Symptoms include narrowed blood vessels, inflammation in artery walls, increased platelet production, and porous blood vessel walls.[5]



(Fig. 2.2) Endothelial Disorder in Metabolic and Cardiovascular Diseases

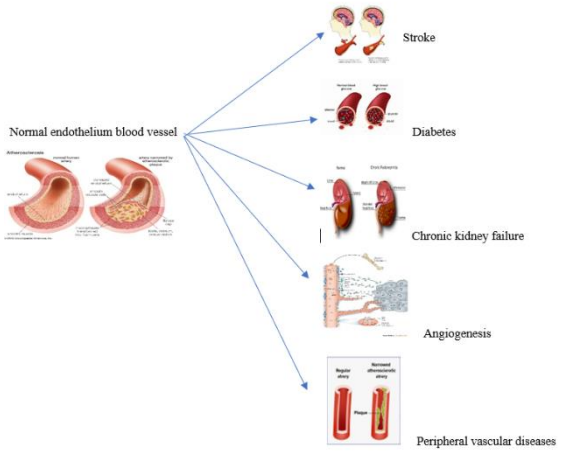
- **Symptoms**

  Angina, or chest pain, is the main symptom of endothelial dysfunction in coronary arteries. This chest pain is the result of your arteries closing when they should be open. The chest pain is often worse during physical activity. Some people develop continued angina even at rest, which can signal a heart attack. Symptoms include unrelenting chest pain, extreme fatigue and shortness of breath. This is a medical emergency that requires immediate treatment.[5]

- **Risk factors**

Certain factors may increase your risk of endothelial dysfunction. Your risk is higher if you have:

1. Diabetes.
2. High blood pressure (hypertension).
3. High blood sugar (hyperglycemia).
4. High cholesterol.
5. Metabolic syndrome.
6. Smoking.
7. Obesity [5,6]



(Fig. 2.3) Endothelial Disfunction Causing Disorders

- **Complications**

Endothelial dysfunction can lead to acute coronary syndrome. This combination of three different types of coronary artery disease increases the risk of plaque rupturing inside a blood vessel. A ruptured plaque can block blood flow to your heart muscle, causing a heart attack.[5]

- **Diagnosis and tests**

Healthcare providers use imaging tests to view blood flow through blood vessels directly. These tests let your healthcare provider check for signs of endothelial dysfunction. These tests include:

1. Electrocardiogram (EKG).
2. Angiogram, including coronary computed tomography angiogram (CCTA).
They can also use certain types of stress imaging to see if there's decreased blood flow through your blood vessels that cause decreased function in your heart. These imaging tests include:
1. Echocardiogram (echo).
2. MRI.
3. Positron emission tomography (PET) scan. [5]

- **Management and treatment**

If you have coronary or peripheral artery disease due to endothelial dysfunction, your healthcare provider may also recommend medications, such as:
1. Aspirin or medications to prevent blood clots.
2. Blood pressure medicines like calcium channel blockers.
3. Cholesterol-lowering drugs like statins.
4. Nitrates to open up blood vessels.
If you have endothelial dysfunction, you can also minimize your symptoms with dietary and lifestyle changes. These include:
1. Eating a heart-healthy diet and getting regular exercise.
2. Limiting alcohol consumption.
3. Losing weight (if needed) and maintaining a healthy weight.
4. Finding healthy ways to manage stress.
5. Getting help to quit smoking and avoiding second hand smoke.
6. Managing conditions like high blood pressure, diabetes and high cholesterol. [5]

3. PHYTOCOMPOUNDS:

Ginseng

Ginseng, an ancient plant native to Asia and North America, is commonly used in oil extracts, tea, tablets, capsules, and dried roots. Extracts have been shown to have anti-obesity, anti-hyperglycemic, anti-hypertensive, insulin sensitization, and anti-hyperlipidemic effects.

MOA

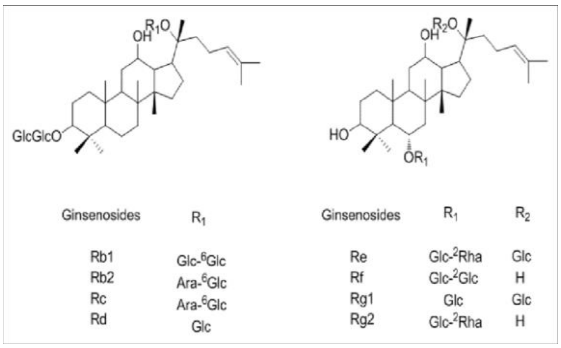
Ginseng enhances eNOS expression, NO production, and NO-dependent vasorelaxation, improving vascular tone by inhibiting arginase activity, increasing NO generation, and enhancing eNOS dimer formation.

Ginseng to the clinic

Clinical trials have investigated the cardio-protective and beneficial effects of Ginseng and its constituents in CVD treatment, with a significant number focusing on hypertension, arterial occlusive diseases, and strokes. One trial found that Panax Ginseng extract (PGE) decreased serum

triglycerides and total cholesterol levels while increasing HDL levels due to its potent antioxidant effects.

Ginseng Plant



Chemical Structure of Ginseng
(Fig. 4.1)

Safety, toxicity, and side effects of ginseng

Ginseng extracts have minimal side effects, with few adverse effects reported after prolonged use. However, a young man experienced hypertension, shortness of breath, dizziness, and concentration issues after three years of Ginseng supplementation. [2, 7,9]

Ginkgo biloba

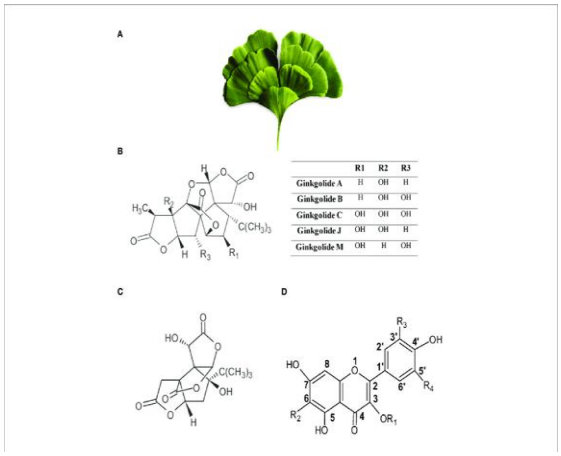
Ginseng extracts have minimal side effects, with few adverse effects reported after prolonged use. However, a young man experienced hypertension, shortness of breath, dizziness, and concentration issues after three years of Ginseng supplementation.

MOA

Ginkgo biloba (GBE) is known for its antioxidant and anti-inflammatory properties, which are beneficial in various diseases. Its vasodilatory and antihypertensive properties can improve cardiovascular health. GBE also exhibits ACE inhibitory activities, cholinergic pathway activation, endothelial health improvement, and serum lipid-lowering activities. It can limit LPS-induced proliferation of VSMCs, regulate inflammatory response in blood vessels, and reduce adipogenesis and lipolysis, leading to lipid accumulation suppression.

Ginkgo biloba to the clinic

Clinical trials have been conducted to test different formulations and doses of Ginkgo biloba leaf extract (GBE) in various diseases, with 7 out of 88 trials focused on vascular diseases. Several ongoing trials assess GBE's protective effects in CVDs. A Phase 3 trial evaluated Rinexin®, an anti-platelet agent for peripheral artery disease, while a Phase 4 trial assessed Ginkgo biloba pills for CHD patients with impaired glucose regulation.



(Fig. 4.2)Ginkgo Biloba with its Chemical Structure

Safety, toxicity, and side effects of ginkgo biloba

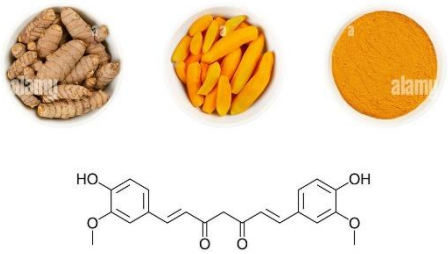
Ginkgo biloba leaf extracts can cause mild adverse effects, such as gastrointestinal upset, headache, dizziness, constipation, and allergic skin reactions. High dosages can cause restlessness, diarrhoea, nausea, vomiting, and weakness. GBEs should be stopped at least 2 weeks before surgical procedures and used with caution during pregnancy, labour, and lactation. They can also decrease plasma concentrations of omeprazole, ritonavir, and tolbutamide and interact with other medications. [2,9]

Curcumin

Curcumin, is a flavonoid compound which is obtained from roots of plant 'Curcuma longa' which is a major component of turmeric. Curcumin is beta-diketone group of carbon double bond with number hydroxy group and methoxy substituent.

MOA

Curcumin basically helps to protect endothelial cells from negative vascular effects which are stimulated by TNF-alpha which modulates P38, signal transducer and activator of transcription-3 (STAT-3) nuclear factor KAPPA-B (NFKB) and C-Jun N-terminal kinase in endothelial cells. It is also reported that Curcumin significantly inhibited TNF-alpha induced lectin like oxidised LDL receptor 1 (LOX-1) and supressed endothelial disfunction against TNF-alpha.
Basically, the authors also determined that curcumin treatment inhibited the formation of ROS along with IKB-alpha and translocation of NF-B. curcumin simultaneously induces eNOS to produce sufficient production and availability of nitrous oxide (NO) for optimal endothelial function. Additionally, it is also found that curcumin reduced the production of ICAM-1 mRNA and its associated protein in human umbilical vein endothelial cells (HUVECs). Curcumin also helps to inhibit the adhesion of leukocyte.
Leukocyte recruitment and adhesion are the hallmarks for vasculature and probably. The first stage in atherosclerotic plague development. When leukocyte adhered to endothelial cells then development and stabilization of local inflammation occurs.



(Fig. 3.3)
Curcumin and its Chemical Structure

Curcumin to the clinic

Brachial artery flow-mediated dilation and aortic pulse-wave velocity are commonly used to assess impaired endothelium-dependent dilation and increased large elastic artery stiffness, which are associated with cardiovascular events and mortality. Curcumin, a polyphenol found in turmeric, has been shown to activate antioxidant transcription, suppress

inflammation, and reduce proliferation, and improve kidney histology in ADPKD models.

Safety, toxicity, and side effects of curcumin

Both turmeric and its main active ingredient, curcumin, are generally considered safe and without any serious side effects. However, some people may experience side effects when they take them in large doses as supplements.

Digestive issues. People may experience mild digestive issues such as bloating, acid reflux, flatulence, and diarrhoea at daily doses exceeding 1,000 mg.

Headache and nausea. Doses of 450 mg or higher may cause headache and nausea in a small number of people.

Skin rash. People have reported a skin rash after taking a dose of 8,000 mg of curcumin or more, but this seems to be very rare [2,3,9]

Ganoderma lucidum

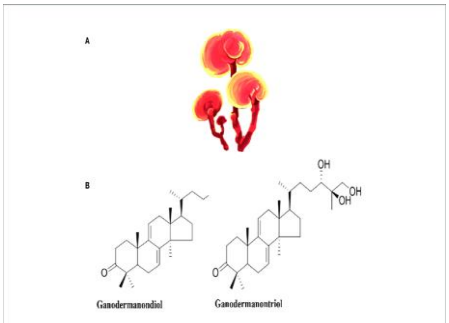
Ganoderma lucidum, also known as lingzhi or reishi, is a mushroom with various bioactive compounds including immunomodulation, anti-oxidation, liver protection, anti-proliferation, and anti-angiogenesis. Its triterpenoids have hepatoprotective, anti-hypertensive, hypo-cholesterolemic, anti-histaminic, anti-tumour, and anti-angiogenic effects.

MOA

G. lucidum, an antioxidant, has been shown to protect against oxidative stress in model organisms like Caenorhabditis elegans and treat hypertension. It also contains ACE inhibitory peptides (ACEIPs) that can inhibit ACE activity. G. lucidum's water extract can reduce body weight, inflammation, and insulin resistance in HFD-fed mice. In a study, G. lucidum spores (GLSP) were found to decrease cholesterol and triglycerides in diabetic rats, attenuating oxidative stress levels and upregulating genes related to lipid metabolism.

Ganoderma lucidum. (A) Ganoderma lucidum (from https://pngtree.com/freepng). (B) Examples of the chemical structure of two Triterpenes from Ganoderma lucidum.[13].

Ganoderma Lucidum and its Chemical Structure (Fig. 3.4)



Ganoderma lucidum to the clinic

Antioxidants are potential therapeutic substances that can prevent atherosclerosis and other diseases. Preclinical studies have shown that G. lucidum constituents possess antioxidant activities, but evidence for their activities in human subjects was lacking. A follow-up study showed an enhancement of plasma total antioxidant markers status and improvement of CHD biomarkers after 10 days of supplementation. A crossover human intervention study found that plasma total antioxidant power was enhanced after the administration of a single dose of G. Lucidum extract. G. lucidum PsP was also examined for its antioxidant properties, showing increased SOD, decreased MDA levels, and reduced counts of circulating endothelial cells and endothelial progenitor cells. A randomized clinical trial found no effect on glycosylated hemoglobin and fasting plasma glucose, and increased risk of mild events. A prospective double-blind, placebo-controlled trial found that G. lucidum failed to provide benefit against cardiovascular disease (CVD) in patients with the metabolic syndrome and not effective in treating elevated blood pressure.

Safety, toxicity, and side effects of ganoderma lucidum

The safety of polysaccharides extracted from G. lucidum fruiting bodies was evaluated in Wistar rats, with no abnormal symptoms, death, or significant differences in body weight or food intake. High doses of G. lucidum polysaccharides modulated immune responses, but did not significantly affect phagocytic function or macrophages. A 12-week trial on 23 dyslipidemic and mild hypertensive volunteers found no effect on clinical chemistry parameters, but symptoms like headache and influenza/running nose were found. Further studies are needed to assess the toxicity, side effects, and safety of G. lucidum for human consumption. [2,9]

Gynostemma Pentaphyllum

Gynostemma pentaphyllum, also known as Jiaogulan, is a climbing vine found in subtropical China, Japan, Myanmar, and India. It is used as a health supplement in beverages, biscuits, face washes, and bath oils. The herb has low genetic diversity and high variation among populations. Its biological effects range from antimicrobial, antioxidant, anticancer, anti-inflammatory, antidiabetic, antilipidemic, neuroprotective, and anti-obesity effects. It has been used to treat hepatitis and hypertension.

MOA

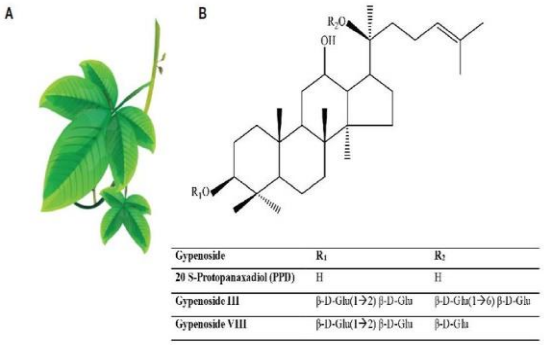
Inflammation can contribute to atherosclerosis and other cardiovascular disease risk factors, making reducing inflammation a protective factor. Gypenoside XLIX from G. pentaphyllum has been studied for its anti-inflammatory properties, inhibiting NF-kB activation through a PPAR-a dependent pathway. However, it also attenuated NF-kB activation and suppressed NO production by inhibiting iNOS activity. Combine, a flavonoid from G. pentaphyllum, has been found to be involved in lipid metabolism, reducing intracellular concentrations of triglyceride and cholesterol, and decreasing lipogenic gene expression.

Gynostemma Pentaphyllum to the Clinic

Few human trials have investigated the therapeutic effects or safety of G. pentaphyllum extracts. Only four studies have used G. Actiponin, an extract of G. pentaphyllum, has been used for weight loss in obese individuals, with no adverse effects. Another study found that G. pentaphyllum water extract inhibited platelet aggregation, suggesting potential for preventing cardiovascular diseases. Anxiety disorders have been linked to an increased risk of developing cardiovascular diseases, and G. pentaphyllum ethanol extract has shown anti-anxiety effects on mice exposed to chronic stress. Studies have shown that G. pentaphyllum tea can improve insulin sensitivity and glycemia in T2DM patients, with no adverse side effects. The current data indicates that G. pentaphyllum is effective in improving insulin sensitivity and blood sugar levels if administered alone and may be enhanced when combined with other medications.

Safety, toxicity and side effects

A study on G. pentaphyllum extract's toxicity on female Sprague-Dawley rats found no toxicity or abnormalities. Long-term administration of a dose up to 750 mg/kg body weight also showed no toxicity. A Phase I clinical trial found no major immune adverse events or biochemical parameters affected by G. pentaphyllum extract. A randomized, double-blind, placebo-controlled clinical trial in 72 healthy adults found no adverse side effects of the ethanolic extract. Overall, G. pentaphyllum consumption seems safe at the doses required for therapeutic effect. [2,9].



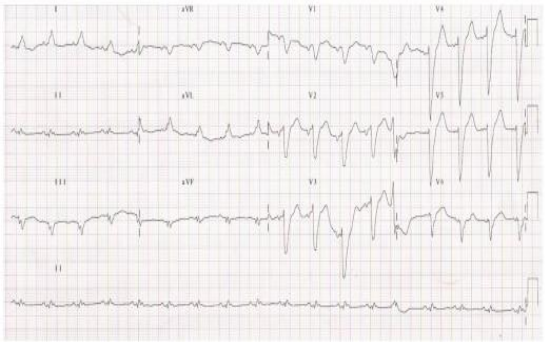
Gypenoside	R_1	R_2
20 S-Protopanaxadiol (PPD)	H	H
Gypenoside III	β-D-Glu(1→2) β-D-Glu	β-D-Glu(1→6) β-D-Glu
Gypenoside VIII	β-D-Glu(1→2) β-D-Glu	β-D-Glu

(Fig. 3.5)
Gynostemma Pentaphyllum with Chemical Structure

CASE STUDY

1st case study

A 67-year-old woman with ischemic heart disease was admitted to the hospital due to chest pain and shock. She was diagnosed with myocardial infarction in April 2009, and was diagnosed with hypertension, diabetes mellitus, dyslipidemia, and smoking. After the infarction, she underwent coronary angiography, which revealed 70% obstruction in the right coronary, anterior descending, and circumflex arteries. Echocardiogram revealed ventricular dysfunction with diffuse hypokinesis. The patient's evolution was asymptomatic until October 2009, when she had a cerebrovascular accident with motor sequela. On December 30, 2009, she experienced severe chest pain for one hour. Laboratory tests revealed hemoglobin, hematocrit, leukocytes, total cholesterol, total cholesterol, triglycerides, CK-MB mass, troponin I, urea, creatinine, sodium, potassium, bicarbonate, and base excess. After cardiac arrest, she had seizures and cardiac arrest, which was reversed in five minutes. A new cardiac arrest occurred 20 minutes later, which was also reversed. After half an hour, a new episode of cardiac arrest occurred, which was irreversible, and the patient died.[11].



(Fig . 4.1)

Electrocardiogram - Sinus rhythm, low voltage of the QRS complex in the frontal plane, electrically inactive area in the inferior wall and left bundle branch block.

2nd case study

Barry, a 47-year-old male with a family history of heart problems and diabetes, was diagnosed with cardiovascular disease (CVD) risk factors such as increased alcohol consumption, poor diet, and slightly elevated cholesterol. His health check was delivered by a white British female PN, who had 8 years of experience and preferred JBS3 over QRISK2. Barry's 10-year risk was 3.1%, and his heart age was estimated at 54, 7 years older than his actual age. The main recommendations were to reduce chocolate biscuit consumption and increase fruit and vegetable intake. Barry implemented these changes three weeks post-health check, and his cholesterol fell to within the normal range. Barry expressed concerns about the health check's depth and the level of understanding it provided. He also expressed concerns about the PN's confidence in delivering the 10-year CVD risk, as he could not fully understand the information. The consultation would have been improved to better understand Barry's situation and provide more comprehensive information. The patient's heart condition was influenced by a misinterpretation of the discussion about event-free survival age, leading to a misconception of his survival age of 73. The practitioner's VSR interview revealed the same misinterpretation. Barry was also confused by the PN's attempt to demonstrate small changes can be effective.[12].

MARKETED FORMULATIONS: [13]

Table. 5.1. Cost of gluco-corticosteroids:

Drug	Dosage	Minimum cost	Maximum Cost
Prednisolone	5mg	4.12	156
	10mg	9.84	66.62
	20mg	17.2	90.00
	40mg	33.81	51.17

Table. 5.2 Cost of anti-hypertensive drugs

Drug	Dosage	Minimum Cost	Maximum Cost
Amlodipine	2.5mg	6.50	27.60
Diltiazem	60mg	20.03	50.40
Atenolol	50mg	6.77	23
Enalapril	5mg	17.95	33.71
Losartan	25mg	16.50	38.35
Valsartan	80mg	41	86
	40mg	70	152.50
Labetalol	100mg	100	137
Olmesartan	20mg	34	116.70
Prazosin	2.5mg	94.60	125.80

COMPARATIVE STUDY

Modern medicine management focuses on minimizing the risk of cardiovascular diseases (CVDs) by addressing major risk factors and minimizing adverse outcomes. In atherosclerosis, traditional therapeutic approaches aim to control hypertension and hyperlipidemia or modulate hemostasis to avoid thrombotic complications. Current conventional therapeutic approaches rely on lowering LDL levels using statins, but pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been approved for use in patients with heart problems. The CANTOS clinical trial (2017) suggests that a combination therapy of statins and canakinumab may be necessary for patients with elevated inflammation. Complementary and alternative medicine (CAM), including herbal remedies, have already tackled the inflammatory aspect of atherosclerosis earlier than the CANTOS study. Modern therapy regimens for hypertension involve controlling BP elevations using multiple antihypertensive drug agents.

Traditional medicine and ethnomedicine have been around since human history, relying on natural resources as medications. Herbal and plant products have been a common source of medications, including aspirin, digoxin, ephedrine, lovastatin, taxol, and reserpine. These plants have been used to find new drugs for treating diseases, such as hypertension treatment. The earliest records of natural drugs, found in Mesopotamia around 2600 BCE, describe the use of around 1000 plant-derived compounds. The Egyptians' Ebers Papyrus, Chinese Materia Medical record, and Indian Ayurvedic record all document the use of natural extracts in therapy. Around 65% of the world population relied on plant-derived traditional medicines in 1985. The

WHO identified 122 compounds from 94 plant species used for various ethnomedical treatments. Commercially, drug production from natural products is a viable commodity, with 39% of new drugs approved between 1983 and 1994 being natural compounds or derived from natural compounds. However, advances in combinatorial chemistry shifted focus from natural products to synthesis at the laboratory bench. Despite this, natural products as drugs or discovery platforms are still alive, with traditional herbal and plant-derived extracts becoming more mainstream.[14].

CONCLUSION

Natural herbs are rich sources of potential therapeutic candidates for various diseases including cardiovascular diseases, neurodegenerative disorders, and metabolic dysregulation. Reprocessing the existing medications for alternative applications is an important way to discover new therapies with known safety profiles. For cardiovascular diseases, the vital components of pathogenesis are ROS production and inflammation, which are targeted by many phytocompounds and existing medications. Although extensive studies have been carried out to determine the vascular protective effects of active phytocompounds reviewed in this paper, there are ongoing developments and research studies on other human diseases. Active phytocompounds isolated from natural resources often face challenges in bioavailability and stability. Thus, improving extraction and formulation techniques to maintain biological activities is crucial. Furthermore, biosafety, long-term bioactivity, degrading properties, interactions with immune cells, the ability to sustainably circulate in humans, and excretion must be thoroughly evaluated before consumption. In addition, further research is needed to minimize the cost of industrial-scale manufacturing, develop better methods for synthesis or extract, and discover the optimal route of administration. New phytochemical agents to treat cardiovascular diseases particularly vascular endothelial cells are expected to surface with the progress of research. This review discusses the therapeutic properties of various plants in treating cardiovascular diseases (CVDs). While these plants have potent properties, clinical benefits have not been confirmed. Safety and toxicity concerns have raised concerns, such as Gingko Biloba. Future studies and clinical trials should investigate the role of different medicinal plants and their mechanisms in CVDs.

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Research Article

A STUDY TO ASSESS PATIENT SAFETY WITH CEFTRIAXONE AND METRONIDAZOLE IN POST-OPERATIVE LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS

Charan C S[1], Raghuveer[2], Najeed S M*[3], Rakshitha M[3], Bilal[4], Hanumanthachar Joshi[5]

[1]Professor, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India.
[2]Assistant professor, Department of Surgery, K R Hospital, Mysuru
[3]Pharm D 5th year students, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.
[4]Assisstant Professor, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India
[5]Principal, SaradaVilas College of Pharmacy, Mysore, Karnataka, India

*Corresponding Author: Najeed S M, Sarada Vilas College of Pharmacy, Krishnamurthy Puram, Mysore-570004. Karnataka, India.

ABSTRACT:

Objectives: To determine the incidence of antibiotic (ceftriaxone and metronidazole) resistance among patients undergoing laparoscopic cholecystectomy. To evaluate drug utilization pattern of post-operative laparoscopic cholecystectomy patients.

Methods: A total of 120 patients meeting the study criteria in surgery department will be enrolled in the study after obtaining the informed consent. All relevant data of the enrolled patients will be collected from various data sources and documented.

Results: A total of 120 study participants from Surgery department. The majority of patient belonged to the age group 36-45(32.5%) represented most of the patients in the study were males (45.8%) compared to females (54.16%)From the result, among 120 patients, (20.83%) were Smokers and (79.16%) were Non-smokers. (96.66%) were prescribed Ceftriaxone and (3.3%) patients were not prescribed Ceftriaxone. A culture sensitivity test was done only on 11 patients where 54.54% of the population were resistant to the drug ceftriaxone and 5 were not detected as resistant and there were no patients resistant to metronidazole. In this study, the most commonly prescribed class of drugs were Analgesics (19.8%), followed by Electrolytes (24.08%), Antibiotics (9.7%), PPI (8.02%), Antiparasitic (6.7%), Antiemetic (7.62%), Vitamin (24.08%) respectively.

Conclusion: In our study, antibiotics, PPI, vitamins and analgesics, drugs are most commonly used drug classes in treating post operative lap.Cholecystectomy. Average number of drugs per prescription was high reflecting polypharmacy. This study helps in evaluating the existing drug use pattern, Evaluating antibiotic resistance with ceftriaxone and metronidazole and to make appropriate interventions. This survey helps to estimate the drug utilisation evaluation of laparoscopic cholecystectomy patients and pattern of antibiotic resistance.

INTRODUCTION:

Cholelithiasis, also known as Gallstones, are calcified collections of digestive fluid that can develop in the gallbladder. Gall bladder is located underneath liver segments 4b and 5 on the inferior side of the hepatic bed. The gallbladder has a maximum length of 10 cm and a physiological capacity of 50 cc of bile(1). Gallstone disease affects more than 20 million Americans, and 80,000 patients are admitted to hospitals each year(4) Cholesterol gallstones, black pigment gallstones, and brown pigment gallstones are the three most prevalent forms. Gallstones made of cholesterol account for 90% of all cases.(1) Gallstones composition varies depending on the etiology These illnesses typically have biliary colic symptoms, such as intermittent attacks of persistent, acute stomach pain in the right upper quadrant (RUQ), which is frequently accompanied by nausea and vomiting, as well as normal physical examination findings and laboratory test results. Vomiting, nausea, and diaphoresis could also be present (1)

Laparoscopic cholecystectomy is a minimally invasive surgical operation performed to remove a damaged gallbladder. (5). A novel third-generation cephalosporin, ceftriaxone exhibits good activity against a wide variety of gram-negative bacteria and mediocre activity against the majority of gram-positive bacteria [7]. Metronidazole is one of the main drugs used to treat anaerobic, protozoal, and

microaerophilic bacterial infections. It is cytotoxic to facultatively anaerobic microorganisms.

MATERIALS AND METHOD:

Study site: The study was conducted in Krishna Rajendra hospital, Mysuru.

Study design: This is a Prospective observational study. The sample size of the study was 120 patients.

Study period: The study was carried out for a period of six months.

Ethical approval: Institutional Ethical Committee of Krishna Rajendra hospital Hospital, Mysore approved the study.

Study criteria:

Inclusion criteria:
1. Adult patients >/=18 years of age.
2. Patients of either gender
3. Participants undergone laparoscopic cholecystectomy and receiving ceftriaxone and metronidazole in their treatment regimen

Exclusion criteria:
1. Patients who are not willing to participate.

2. Patients with severe medical conditions that may interfere with the study or pose a safety risk.

3. Pregnant and lactating women

Source of data: Medical and Medication records of the patient. Interviewing patient and caretaker. Communicating with concerned clinicians and health care professionals. Telephonic contact with patients and/or physicians if necessary.

Study procedure: The study involved the following steps: -

1. Preparation of informed consent form (ICF): An informed consent form was suitably designed both in English (Annexure 1) as well as in Kannada (Annexure 2) to obtain consent from patients who volunteered for the study and fulfilled the study criteria. The ICF was reviewed and approved by the institutional ethics committee. The patient was explained about the study and consent was obtained after they voluntarily agreed after being aware of every important aspect regarding the study. For those patients who were illiterate, the study was discussed with them, and consent was obtained from caretakers.

2. Preparation of data collection form (DCF): A specially designed data collection form (Annexure 3) was designed for the study. The particulars included demographic details like name, age, gender, family history, social habits (smoking, tobacco chewing, and alcoholism), diet, weight, height, and body surface area. Clinical data such as diagnosis, past medical history, past medication history, Therapeutic data such as the name of the drug, dose, frequency, duration, route of administration, details on the supportive medication used, premedication, and discharge medications. It also contains the details of laboratory test results.

3. Patient enrollment: Patients fulfilling the study criteria were enrolled in the study after obtaining informed consent.

4. Data collection: All relevant details of the enrolled patients were obtained from various data sources and documented in the data collection form.

5. Statistical analysis: the collected data were entered and assembled in Microsoft excel. The data was analysed using descriptive statistical analysis with the help of Microsoft excel to calculate the quality of life in study population, to determine and divide the study population according to the demographic details and clinical characteristics. Frequency and percentage of Resistance in different demographic categories was calculated and expressed in suitable charts

RESULTS:

A total of 120 study participants from Surgery department who met our inclusion criteria and had been through laparoscopic cholecystectomy were enrolled in the study.

Demographic Data: The average age of the patient was found to be 41.01 . The majority of patient belonged to the age group 36-45(32.5%). Most of the patients in the study were males (45.8%) compared to females(54.16%) among 120 patients, 79.16% were Non-smokers and 81.6% were Non-alcoholic.

Ceftriaxone treatment: Among 120 patients, the antibiotic Ceftriaxone 1g IV was distributed; 96.66%

Ceftriaxone Treatment	No. of patients	Percentage
Prescribed	116	96.66%
Not Prescribed	4	3.3%
Total	120	100%

Table 1: Representation of the total Study population that received Ceftriaxone treatment

Distribution of ceftriaxone therapy based on age group categorization was found to be the majority of patients who received ceftriaxone therapy were under the age 36-45(32.5%)

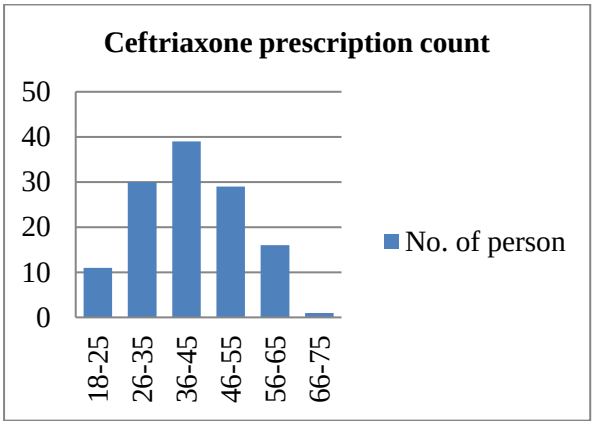

Figure 1: Representation of Ceftriaxone Prescription Count based on age group

Culture sensitivity test: From the result, among 120 patients, a Culture sensitivity test was done on 11 patients (9.16%)

Culture sensitivity test	No. of patients	Percentage
Wound culture conducted	11	9.16%
Wound culture not conducted	109	90.83 %
Total	120	100%

Table 2: Total study Population receiving Ceftriaxone treatment, undergone Culture sensitivity test count

Resistance to Ceftriaxone: Culture sensitivity test was done only on 11 patients where 54.54% (n=6) of the population were resistant to the drug ceftriaxone

Resistance	No. of patients	Percentage
Resistant to Ceftriaxone	6	54.54%
Not resistant to ceftriaxone	5	45.46%
Total	11	100%

Table 3: The study population underwent a Culture sensitivity test-detected to be resistant to Ceftriaxone count

Resistant to the drug Ceftriaxone based on Organism strains: The strains of organisms that exhibit Ceftriaxone resistance that is gram-negative bacteria *Escherichia coli* (n=4) and gram-negative bacteria *Pseudomonas aeruginosa* (n=2).

Metronidazole treatment: antibiotic Metronidazole500mg IV was distributed; 83.33% were prescribed

Metronidazole treatment	No. of patients	Percentage
Prescribed	100	83.33%
Not Prescribed	20	16.67%
Total	120	100%

Table 4: Representation of the total Study population that received Metronidazole treatment

Resistance to Metronidazole: A Culture sensitivity test was done only on 11 patients where there were no patients resistant to metronidazole

Drug Utilisation Pattern: From the study population total of 1495 drugs were prescribed the average number of drugs prescribed per prescription was found to be 12.45. commonly prescribed class of drugs were Analgesics (19.8%), followed by Electrolytes (24.08%), Antibiotics (9.7%), PPI (8.02%), Antiparasitic (6.7%), Antiemetic (7.62%), Vitamin (24.08%) respectively.

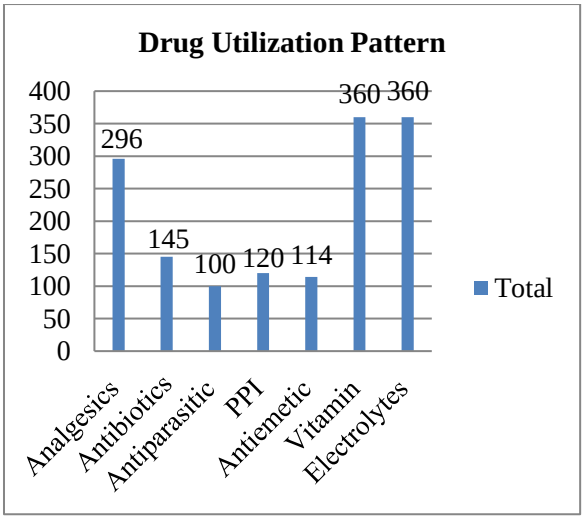

Figure 2: Representation of Distribution of drug utilization pattern

Conclusion:

In our study, antibiotics, PPI, vitamins and analgesics, drugs are most commonly used drug classes in Treating Post operative lap. Cholecystectomy. Evaluating antibiotic resistance with ceftriaxone and metronidazole, and to make appropriate interventions required to provide optimum healthcare services to the community. Ceftriaxone has broader and stronger gram-negative coverage then first or second-generation cephalosporins, and . Metronidazole is used to treat or prevent certain infections that may occur during surgery. Culture sensitivity test was done only on 11 patients 6 were resistant to the drug ceftriaxone and none of them were resistance to metronidazole since ceftriaxone is largely used than metronidazole. This survey helps to estimate the drug utilisation evaluation of laparoscopic cholecystectomy patients, And pattern of antibiotic resistance.

ACKNOWLEDGEMENT:

The authors are thankful to our mentor **Dr. Charan C S**, Associate Professor and Head, Department of Pharmaceutics, SVCP, and all the faculty members of the Department of Pharmacy Practice, SVCP, Mysuru. We also thank **Dr. Hanumanthachar Joshi, Principal, SVCP, Mysuru**, and We whole heartedly thank our co-guide **Dr.Bilal**, assistant professor, department of pharmacy practice, Sarada Vilas College of Pharmacy, for his continuous support. Special thanks to **Dr. Ravindra P Choudhary** for his support and guidance which helped us complete our project work. Our special thanks to all my friends for their moral support and suggestion which helped us complete our project work.

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Review Article

RIBOSE 5 PHOSPHATE ISOMERASE DEFICIENCY: A RAREMETABOLIC DISORDER

Saddam Shamashuddin Maner, Pranoti Pralhad Jadhav, Deepti Dharmendra Kamble, Atharva Vinod Hande, Aarti A. Varne*

*Department of Pharmaceutical Chemistry, Anandi Pharmacy College, Kalambe tarf Kale, Kolhapur, Maharashtra, India

ABSTRACT:

An enzymopathy of the pentose phosphate pathway is ribose 5-phosphate isomerase (RPI) deficiency. One rare condition that no medication can prevent is ribose 5-phosphate isomerase. These diseases, which cause the brain's mucus and white matter to build abnormally and impair brain function, are the most underappreciated. And as a result, people pass away. In this condition, the amount of cerebral white matter increases and decreases, elevating the D-ribitol level. Residue exchange cannot be entirely blamed for the RPI activity observed in patient cells. The rarest conceivable disease, ribose-5-phosphate isomerase deficiency, is a malfunction in the pentose phosphate pathway (PPP) with only one confirmed case. Because ribose-5-phosphate isomerase is an enzyme involved in the pentose phosphate pathway, mutations in this enzyme can cause ribose 5 phosphate isomerase deficiency, the most uncommon condition. Ribose 5 phosphate utilizes the purine synthesis pathway to initiate the production of phosphoribosyl pyrophosphate (PRPP). Ribose and ribose phosphate are the products as well as the intermediates of the pentose phosphate pathway.A fairly uncommon, hereditary pentose phosphate metabolism condition called ribose-5-P isomerase deficiency is characterized by a progressive leukoencephalopathy and significantly elevated levels of ribitol and D-arabitol in the brain and bodily fluids. Unstable ribose 5 phosphate enzyme synthesis is the cause of ribose 5 phosphate isomerase. Any disease that affects the human body, such as optic atrophy, cerebellar ataxia, seizures, or epilepsy, is the cause of them. Treatment for diseases resulting from ribose 5 phosphate isomerase problem is utilized to diagnose them.

Keywords: ribose-5-phosphate isomerase deficiency, rare metabolic disease, carbohydrate metabolism, pentose phosphate pathway.

INTRODUCTION:

The most uncommon condition is ribose 5 phosphate isomerase (RPI) deficiency, which is brought on by mutations in the enzyme ribose-5-phosphate isomerase, which is involved in the pentose phosphate pathway. Phosphoribosyl pyrophosphate (PRPP) is produced by ribose 5 phosphate, which is initiated via the purine synthesis route. Both the product and the intermediate of the pentose phosphate pathway are ribose and ribose phosphate. The PPP's novel inborn error known as RPI deficiency (i.e. rpi). Deficient conversion of ribulose 5-phosphate to ribose-5-phosphate results in buildup of pentoses and pentose phosphates, which in turn lead to accumulation of ribitol and D-arabitol as metabolic end products. This is the most likely explanation for the biochemical anomalies observed in our patient/patient. Ribose 5 phosphate isomerase has only been diagnosed in three cases in the last 27 years. The world's rarest sickness right now is RPI deficiency. The gene that causes or results in the ribose 5 phosphate isomerase deficiency. Additionally, these are a genetic condition.[1]

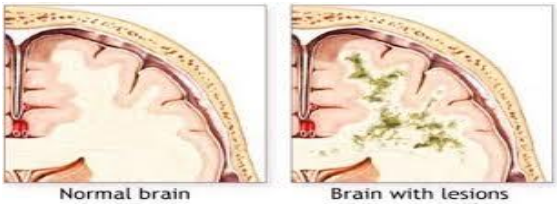
HISTORY OF RIBOSE 5 PHOSPHATE ISOMERASE DEFICIENCY

A rare disorder called ribose-5-phosphate isomerase deficiency is caused by a mutation in this enzyme. Only one patient with the disease is known to exist; they were diagnosed in 1999. It has been determined that two mutations working together are the cause. Van der Knaap and colleagues discovered the first

case of RPI deficiency in 1999. The boy, then 14 years old, had a frameshift mutation in one allele that caused developmental delay, leukoencephalopathy, seizures, psychomotor retardation, and irregular polyol metabolism. A male born in 1984 to unrelated, healthy parents was the first patient. The patient experienced psychomotor retardation in infancy and began having epilepsy at the age of 4. Beginning at age 7, there was a gradual decline in neurological function, accompanied by notable cerebellar ataxis, mild sensorimotor neuropathy, optic atrophy, and some spasticity. Internal organ organ dysfunction was not observed. D-ribitol and D-arabitol levels were elevated and there were extensive abnormalities of the cerebral white matter in the MRI scans performed at ages 11 and 14.

Upon reviewing the case of the 14-year-old boy in 1999, van der Knaap and associates identified the following symptoms as indicative of RPI deficiency: abnormal polyol metabolism, epilepsy, developmental delay, and subtle psychomotor regression. Subsequently, a second case involving an 18-year-old man with diffuse white matter abnormality, psychomotor regression, and seizures was reported by Naik and colleagues. In 2018, Sklower Brooks and associates reported a third case involving a child who had psychomotor delays and neonatal onset leukoencephalopathy. Kaur and colleagues reported a fourth case in 2019 that included increasing urine polyols (ribitol and arabitol) and progressive leukoencephalopathy

Fig. no. 01-The Normal Brain and Ribose 5



Phosphate Isomerase Deficiency Brain

TYPES OF RIBOSE 5 PHOSPHATE ISOMERASE – (RPiA AND RPiB)

1. RPiA gene

The gene for protein coding is called RPIA (ribose 5-Phosphate Isomerase A). A number of illnesses are linked to RPIA, such as glutathione synthetase and ribose 5-phosphate isomerase deficiencies. Using ribose-5-phosphate isomerase A (RpiA), ribose-5-phosphate and ribulose-5-phosphate can be interconverted. Also referred to as RPIA, ribose-5-phosphate isomerase A is an enzyme that is essential to the pentose phosphate pathway (PPP), a metabolic pathway that produces ribose-5-phosphate, which is used in nucleotide synthesis, and NADPH (reduced nicotinamide adenine dinucleotide phosphate).

RPIA is the enzyme that catalyzes the conversion of ribulose-5-phosphate to ribose-5-phosphate. This is a crucial stage in the pentose phosphate pathway's non-oxidative phase, which is in charge of different sugar phosphates' interconversion.

Entire Nucleotide Synthesis Process: The result of RPIA's activity is ribose-5-phosphate, which is a building block for the synthesis of nucleotides, such as DNA and RNA. RPIA is therefore crucial for cell division and growth.

2. RPiB gene

The pentose phosphate pathway is a metabolic pathway that produces ribose-5-phosphate, a vital component for nucleotide biosynthesis and other cellular functions. Ribose-5-phosphate isomerase B (RpiB) is an enzyme involved in this pathway. Particularly, ribulose-5-phosphate (R5P) and ribose-5-phosphate (Ru5P) interconversion is catalyzed by RpiB. An essential component for the synthesis of DNA and RNA is ribose-5-phosphate. The activity of RpiB guarantees that nucleotide biosynthesis has access to a sufficient amount of ribose-5-phosphate. An essential component for the synthesis of DNA and RNA is ribose-5-phosphate. The activity of RpiB guarantees that nucleotide biosynthesis has access to a sufficient amount of ribose-5-phosphate. Since nucleotides are the fundamental units of genetic material, RpiB is an essential enzyme for the division and proliferation of cells. Numerous organisms, including bacteria and plants, contain RpiB, whose activity is essential for preserving the nucleotide pools within cells. The enzyme is essential for maintaining equilibrium between the synthesis of ribose-5-phosphate and other cellular metabolic processes.

Application of the Ribose-5-Phosphate

1) RPI is a key enzyme in a pentose phosphate pathway.
2) Ribose 5 phosphate is a precursor for the synthesis of Neucleotide and RNA and DNA.

3) The ribose 5 phosphate is key intermediate in the synthesis of pentose sugar which are important for various cellular processes.
4) They also useful in a glycolysis and gluconeogenesis which are central metabolic pathway to regulate glucose metabolism in cells.
5) They useful in biotechnology and biofuel production.
6) They are also used to diagnosing and monitoring various disease.

Mechanism of ribose 5 phosphate isomerase- (Pentose Phosphate Pathway)

Ribose 5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) are the products of the pentose phosphate pathway (PPP), a glucose-oxidizing pathway that proceeds concurrently with upper glycolysis. In the cytoplasm of the cell, the pentose phosphate pathway is active. A) the oxidative phase and B) the non-oxidative phase make up these stages.

A) Oxidative phase: Concomitant production of NADPH and the conversion of glucose-6-phosphate to ribulose-5-phosphate characterize this phase.

B) Non-oxidative Phase: This stage is in charge of the interconversion of different sugar phosphates, such as ribose-5-phosphate and ribulose-5-phosphate, as well as other sugars.

- **Significance of PPP**

Red blood cells, adipose tissue, and the liver are examples of tissues with high biosynthetic demands, where the PPP is especially significant. Additionally, it is essential for the synthesis of fatty acids and the production of NADPH in the defenses against oxidative damage.

- **Application of PPP**

Knowing the PPP is important for a number of industries, including biotechnology, biomedicine, and the production of biofuels, since it is a vital pathway for the synthesis of NADPH, which is needed for these and other bioprocesses. Cellular redox balance is crucially maintained by the PPP, an essential metabolic pathway that contributes to the energy and biosynthetic needs of cells.

Ribose 5 Phosphate Isomerase

A rare genetic condition known as ribose-5-phosphate isomerase deficiency affects the pentose phosphate pathway, which provides ribose-5-phosphate—a necessary molecule for the synthesis of DNA and RNA—by stimulating the pathway. Intellectual disability, seizures, and developmental delay are just a few of the symptoms that this condition can cause. In the pentose phosphate pathway, an enzyme called ribose-5-phosphate isomerase (Rpi) catalyzes the change from ribulose-5-phosphate to ribose-5-phosphate. In the interconversion of different sugar phosphates, this enzyme is essential. A sequence of interactions between the substrate and the enzyme, as well as chemical reactions, are involved in how Rpi catalyzes this reaction.

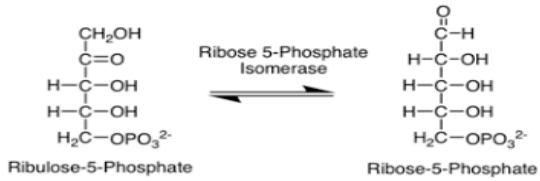


Fig. no. 02- Conversion of ribulose-5-phosphate to ribose-5-phosphate

The conversion can be summarized as follows:

1) When Rpi is present, ribulose-5-phosphate goes through an isomerization reaction.

2) A carbonyl group shift occurs during the reaction, converting a ketose (ribulose-5-phosphate) into an aldose (ribose-5-phosphate). This enzyme's unique mechanism is based on the creation of an enzyme-substrate complex and the utilization of catalytic residues in the enzyme's active site to speed up the isomerization process. The pentose phosphate pathway is used to prepare the ribose 5 phosphate isomerase. This process yields a variety of materials, including coenzymes, DNA, RNA, and nucleotides.

- **Symptoms of Ribose 5 Phosphate isomerase-**
  - Optic Atrophy
  - Nystagmus
  - Cerebellar Ataxia
  - Seizures
  - Spasticity
  - Leukoencephalopathy (Brain White Matter Disease)
  - Global Developmental Delay

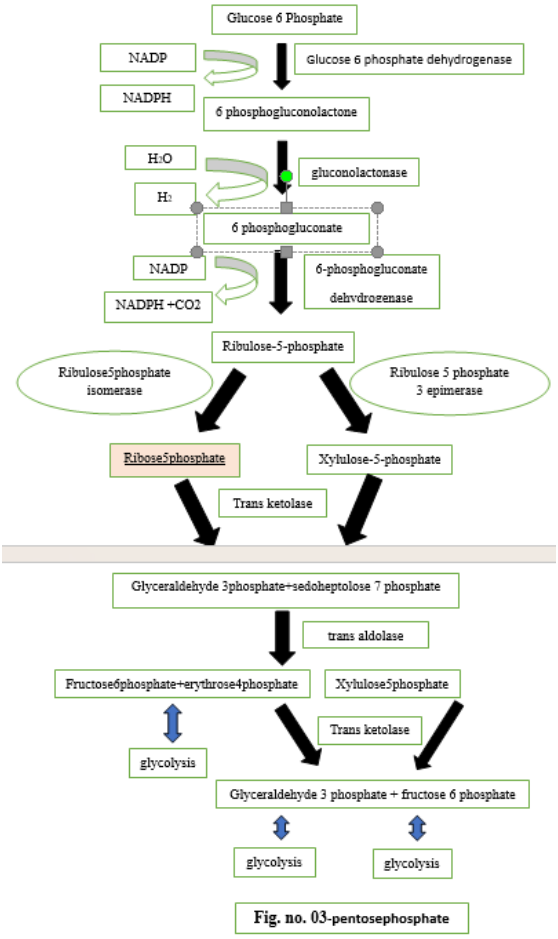


Fig. no. 03-pentosephosphate

Those who suffer from leukoencephalopathy in the current generation have defects in the Pentose Phosphate Pathway (PPP), or RPI Deficiency, as well as highly elevated levels of ribitol and D-arabitol in their body fluid and brain. In contrast, a recent report revealed that the patient had abnormal polyol levels in her bodily fluids, a deficiency in transaldolase, and other defects in the pentose phosphate pathway (PPP).

Diagnosis of ribose 5 phosphate isomerase deficiency

The diagnosis of these disorder is done without the following symptoms-
1)Developmental Delay
2)Epilepsy
3)Psychomotor Regression
4)Leukoencephalopathy
5)Abnormal Polyol metabolism
6)Seizures
7)Cerebellar Ataxia

TREATMENT:

There is no current specific treatment for RPI deficiency. But the symptoms of RPID can be managed by following ways:

OPTIC ATROPHY:

A medical condition called optic atrophy is defined by the degeneration or damage of the optic nerve, which can result in either a partial or total loss of vision. Numerous underlying diseases, including multiple sclerosis, trauma, glaucoma, and genetic factors, may be the cause. Depending on the underlying cause, treatment options may involve managing the primary condition or utilizing low-vision aids to enhance the quality of life for the affected individuals.

CAUSES

Nerve fibres that transmit impulses to your brain make up your optic nerve. In the case of optic atrophy, something is interfering with your optic nerve's ability to transmit these impulses. Many factors can cause this interference, including:

i. **Lack of proper blood flow (vascular/ischemia):** This is the most common cause of optic nerve atrophy.

ii. **Conditions that you're born with or inherit (congenital):** One condition, Leber's hereditary optic neuropathy, causes you to lose vision in one eye first and then the other.

iii. **Damage from inflammation, either from other diseases or swelling in the optic nerve itself:** One cause is optic neuritis, which is inflammation of your optic nerve. Another is hydrocephalus, or fluid collection in your brain.

iv. **Damage from diseases of the retina:** Retinal diseases include diabetes-related retinopathy and retinal vein occlusion.

SYMPTOMS

Optic atrophy symptoms relate to changes in vision, including:

i. Blurred vision or a reduction in sharpness of vision.
ii. Difficulties with peripheral vision.
iii. Difficulties with colour vision.

CEREBELLAR ATAXIA:

A neurological condition known as cerebellar ataxia affects the cerebellum, which is in charge of coordinating voluntary muscle movements, balance, and posture. Cerebral ataxia is a condition characterized by difficulties with balance and walking, slurred speech, and muscle weakness. It can be caused by genetic mutation, acquired conditions such as stroke, tumor, or multiple sclerosis, and alcohol abuse. They suffer from both hereditary and non-genetic forms of cerebral ataxia, as well as uncoordinated movement brought on by a cerebellar lesion. The medication ACETAZOLAMIDE can be used to treat episodic ataxia, and lifestyle changes can also be recommended. Antibiotics and antivirals can be used to treat acquired ataxia. (12,13)

CAUSES

Damage to the part of your brain that controls muscle coordination (cerebellum) or its connections can cause ataxia.

i. **Alcohol.** Long-term excess alcohol intake may cause persistent ataxia. It's possible it may improve by avoiding alcohol completely.
ii. **Medications.** Ataxia is a potential side effect of certain medications, especially barbiturates, such as phenobarbital; sedatives, such as benzodiazepines; antiepileptic drugs, such as phenytoin; and some types of chemotherapy.
iii. **Thyroid problems.** Hypothyroidism and hypoparathyroidism can cause ataxia.
iv. **COVID-19 infection**. Ataxia most commonly results from severe COVID-19 cases.
v. **Hereditary causes**:Some types of ataxia and some conditions that cause ataxia are hereditary.

SYMPTOMS

Ataxia can develop over time or come on suddenly. Ataxia is a sign of several neurological disorders and can cause:

i. Poor coordination
ii. Walking unsteadily or with the feet set wide apart
iii. Poor balance
iv. Difficulty with fine motor tasks, such as eating, writing or buttoning a shirt
v. Involuntary back-and-forth eye movements (nystagmus)
vi. Difficulty swallowing

(Fig. no. 04) Cerebellar Ataxia

SEIZURES:

MRI, CT, CAT, and EEG scans are among the tests that recommend an early diagnosis. Anti-epileptic medications and weight loss are part of the treatment. Uncontrollably abrupt electrical disruptions in the brain that can result in a variety of symptoms are known as seizures. Usually, they fall into one of two categories: a) Partial seizures; b) Generalized seizures. (5,6)

CAUSES

Seizures can have various causes, including:

i. **Epilepsy:** A neurological disorder where recurrent seizures occur without an identifiable trigger.
ii. **Brain injury:** Traumatic brain injury, stroke, or brain tumors can lead to seizures.
iii. **Metabolic disorders:** Imbalances in blood sugar, electrolytes, or other metabolic factors can trigger seizures.
iv. **Genetics**: Some individuals have a genetic predisposition to seizures.
v. **Fevers**: High fevers, especially in children, can cause febrile seizures.
vi. **Brain abnormalities:** Structural issues in the brain, such as malformations or lesions, can lead to seizures.

SYMPTOMS

Seizures symptoms vary and can include,

i. Sudden Change In Awareness Or Full Loss Of Consciousness.
ii. Involuntary Twitching Or Stiffness In The Body Or Severe Stiffening.
iii. Limb Shaking With Loss Of Consciousness (A Convulsion.)

SPASTICITY:

Daily stretching exercises help to improve motor flexibility and can help to decrease it. A medical condition called spasticity is characterized by stiffness or elevated muscle tone. It is frequently linked to diseases like multiple sclerosis, stroke, cerebral palsy, and spinal cord injuries. Damage to the central nervous system is the cause of them. Anti-spasticity and muscle relaxant medications can lessen the likelihood of spasticity. Another treatment option for spasticity is a change in lifestyle that includes a balanced diet and frequent exercise. (11)

CAUSES

Spasticity is a condition characterized by muscle stiffness and involuntary muscle contractions. It can be caused by various factors, including:

Neurological Disorders: Spasticity is often associated with neurological conditions such as multiple sclerosis, cerebral palsy, stroke, and spinal cord injury. These conditions can disrupt the normal communication between the brain and muscles, leading to spasticity.

Brain and Spinal Cord Injuries: Traumatic injuries to the brain or spinal cord can damage the nerve pathways that control muscle function, resulting in spasticity.

Stroke: When a stroke occurs, it can damage specific areas of the brain, leading to spasticity as a potential complication.

Multiple Sclerosis: This autoimmune disease affects the central nervous system and can result in spasticity due to the damage to nerve fibers.

Cerebral Palsy: Spasticity is a common symptom in individuals with cerebral palsy, a condition that affects movement and muscle coordination from an early age.

SYMPTOMS: Symptoms of spasticity can vary from being mild stiffness or tightening of muscles to painful and uncontrollable spasms. Pain or tightness in joints is also common in spasticity.

i. Muscle stiffness, causing movements to be less precise and making certain tasks difficult to perform.
ii. Muscle spasms, causing uncontrollable and often painful muscle contractions.
iii. Involuntary crossing of the legs.
iv. Muscle and joint deformities.

LEUKOENCEPHALOPATHY:

A class of diseases known as leukoencephalopathy mainly affect the brain's white matter. staying away from medications that affect the immune system. Leukoencephalopathies come in a variety of forms and can be brought on by a number of things, such as genetic mutations, infections, toxins, or underlying medical conditions. Typical leukoencephalopathies include.(7,8)

1)Metachromatic leukodystrophy
2)Adrenoleukodystrophy (ALD)
3)Multiple sclerosis (MS)
4)Progressive multifocal leukoencephalopathy (PML)
5)Canavan disease

CAUSES

Genetic Mutations: Some forms of leukoencephalopathy are caused by genetic mutations that affect the development and maintenance of the white matter in the brain. Examples include X-linked leukoencephalopathy and leukodystrophies.

Metabolic Disorders: Certain metabolic disorders can lead to the accumulation of toxic substances in the brain, damaging the white matter. Conditions like Canavan disease and adrenoleukodystrophy fall into this category.

Infections: Infections of the central nervous system, such as progressive multifocal leukoencephalopathy (PML), can lead to leukoencephalopathy.

Autoimmune Disorders: Conditions like multiple sclerosis (MS) involve an autoimmune attack on the

white matter of the brain, resulting in demyelination and leukoencephalopathy.

Toxic Exposure: Exposure to toxic substances like certain drugs, solvents, or heavy metals can damage the white matter and result in leukoencephalopathy.

SYMPTOMS

Symptoms may include any of the following:

i. Loss of coordination, clumsiness.
ii. Loss of language ability (aphasia)
iii. Memory loss.
iv. Vision problems.
v. Weakness of the legs and arms that gets worse.

NYSTAGMUS:

The medical condition known as nystagmus is characterized by rapid, repetitive, and involuntary eye movements. These eye movements can be rotary, up and down (vertical), or side to side (horizontal). Nystagmus may develop later in life or be congenital, meaning it is present from birth. It could have a number of underlying causes, such as inner ear issues, neurological conditions, or specific drugs. Nystagmus can impair balance and coordination in addition to reducing vision. Depending on the underlying cause, there may be several treatment options available, such as treating the core problem or corrective lenses to enhance vision. To determine the cause of the action, routine eye exams are advised.(9,10)

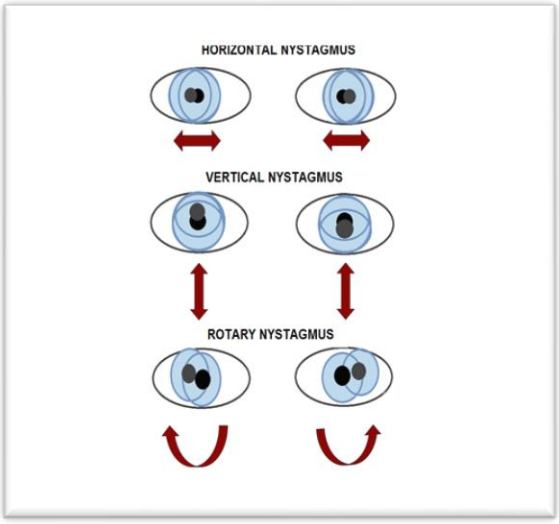


Fig. no 05-Nystagmus

CAUSES

Nystagmus is an involuntary, rhythmic eye movement. It can have various causes, including:

i. **Inner ear problems (vestibular nystagmus):** Often related to issues with the inner ear's balance system, such as benign paroxysmal positional vertigo (BPPV) or Meniere's disease.
ii. **Vision problems (optokinetic nystagmus):** Occurs when the eyes attempt to track a moving object but can't keep up, as in reading while moving in a car.
iii. **Neurological conditions:** Nystagmus can be a symptom of neurological disorders like multiple sclerosis or brainstem lesions.
iv. **Medications or drugs:** Certain medications or substances can cause nystagmus as a side effect.

SYMPTOMS

i. Involuntary eye movement, often side-to-side or up-and-down.
ii. Reduced vision, especially when the eyes are not stable.
iii. Dizziness or vertigo, which can be triggered by the eye movements.
iv. Oscillopsia, a perception that stationary objects are moving.

EPILEPSY

The neurological condition known as epilepsy is typified by recurrent seizures, which are abrupt, uncontrollable electrical disruptions in the brain. Since epilepsy is a chronic illness, managing it may require making lifestyle adjustments such as getting enough sleep, controlling stress, and avoiding triggers. The length and severity of these seizures can vary. Brain traumas, infections, and genetic factors can all contribute to epilepsy.

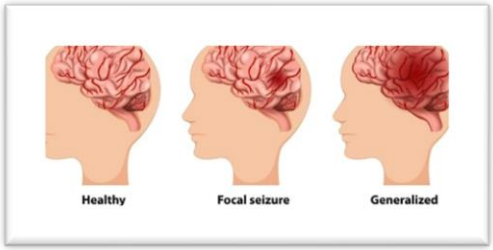
They can be diagnosed using imaging studies like MRIs and CT scans, medical histories, and ECG tests. A person's ability to drive, work, and engage in certain activities can all be impacted by epilepsy. For this reason, having a strong support network and medical professionals on hand can be extremely beneficial.(5,6)

CAUSES

i. **Idiopathic:** In many cases, the exact cause is unknown, and this is referred to as idiopathic epilepsy. It often has a genetic basis.
ii. **Symptomatic:** Epilepsy can be a symptom of an underlying condition or injury, such as brain tumors, head injuries, strokes, or infections like encephalitis or meningitis.
iii. **Genetic:** Some forms of epilepsy have a strong genetic component and can be passed down through families.
iv. **Structural:** Abnormalities in the structure of the brain, such as malformations or developmental disorders, can lead to epilepsy.
v. **Metabolic:** Imbalances in the body's chemical processes can trigger seizures. These metabolic disorders are relatively rare but can lead to epilepsy.
vi. **Febrile:** Febrile seizures occur in young children during a high fever. While they are usually harmless, they can be a precursor to epilepsy in some cases.

SYMPTOMS-

i. Musal Contaction
ii. Loss Of Conciousnes
iii. Anxiety
iv. Staring
v. Weakness



(Fig. no. 06) Epilepsy

CONCLUSION

An innovative inborn error in the PPP is RPI deficiency. The most likely explanation for our patient's biochemical abnormalities is that pentoses and pentose phosphates accumulate due to insufficient conversion of ribulose 5-phosphate into ribose-5-phosphate, which in turn accumulates ribitol and darabitol as metabolic end products. Mutations in the enzyme ribose-5-phosphate isomerase, which is involved in the pentose phosphate pathway, result in ribose-5-phosphate isomerase deficiency, or RPI deficiency, a disorder that affects people. A rare genetic condition known as ribose-5-phosphate isomerase deficiency affects the pentose phosphate pathway, resulting in a shortage of the enzyme ribose-5-phosphate isomerase. Numerous symptoms, such as anemia, developmental delays, and other health problems, may arise from this.In conclusion, for people with this condition to enhance their quality of life and manage the related health challenges, early diagnosis and appropriate medical management are essential. Because of this combination, it was discovered that different tissues and cell types had different RPI activity. Higher levels of ribitol and arabitol in a metabolic profile, along with variations in polyol profiles, are features of the RPI deficiency. Other symptoms include leukoencephalopathy and neuropathy, which could be brought on by an excess of ribitol and arabitol or possibly by a deficiency of ribose-5-phosphate during the synthesis of RNA.A pentose phosphate pathway enzymopathy is ribose 5-phosphate isomerase (RPI) deficiency. It is one of the rarest human disorders, with only one diagnosed case, and presents with progressive leukoencephalopathy and peripheral neuropathy.

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Review Article

TOXICITY PROFILE RELATED TO IMMUNE CHECK POINT INHIBITORS: A COMPREHENSIVE REVIEW

Prajwal B[1*], Snehashree K A[1], Charan C S[2], Umesh M[3], Hanumanthachar Joshi[4]
[1]5th PharmD, Sarada Vilas College of Pharmacy , Mysuru
[2]Head, Department of Pharmacy Practice, SVCP, Mysuru
[3]Associate Professor, Department of Pharmacy Practice, SVCP, Mysuru
[4]Principal,Sarada Vilas College of Pharmacy , Mysuru
Corresponding Author: Prajwal B, Email:prajwalb2007@gmail.com

ABSTRACT:

Immunotherapies are changing the scope of advanced solid tumour treatment. These molecules that increase the endogenous immune response against molecules that increase the endogenous immune response against tumours. They have revolutionized the field of oncology. Immune checkpoint inhibitors are monoclonal antibodies that are used to treat over one in three cancer patients, checkpoint inhibitors, such as CTLA-4 or PD1/PD-L1 monoclonal antibodies, and CSF-1R antibodies. Cancer immunotherapies have unique toxicity profile different from other cancer therapies, which presents difficult for physician in ruling out and addressing adverse effects produced by inflammation brought immune response activation. Any organ or system in the body may have adverse effects; however, GI, dermatologic, hepatic, endocrine, and pulmonary toxicities are the most frequent. Any changes should raise an alert that they are related to the medication. Immune-related adverse effects (irAEs) vary with incidence and onset depending on the type and dosage of Immune check point inhibitors used. Checkpoint inhibitors therapy is frequently continued even in the event of minor irAEs. However, fatal results have been recorded in instances involving moderate to severe irAEs, and these toxicities require early detection along with suitable care. They can additionally lead to life-threatening decreases in organ function and health related quality of life (HRQL).

KEY WORDS: IMMUNOTHERPY, CHECK POINT INHIBITORS, irAEs, CTLA-4 OR PD1/PD-L1

INTRODUCTION:

Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Cancer develops due to genetic mutations that accumulate over time, often triggered by factors such as genetic predisposition, environmental exposures, or lifestyle choices. Traditional cancer treatments include surgery, chemotherapy, and radiation. Developments in Immunotherapy have led to targeted therapies with more effective outcomes.

Immunotherapy is a type of cancer treatment that strengthens the immune system of patients. Immunotherapy can alter or strengthen the immune system's function to enable it to recognize and fight cancerous cells.

The immune system identifies and eliminates abnormal cells as part of its normal function, and it probably stops or slows the growth of many malignancies. For example, immune cells have been observed in and surrounding tumours on occasionally.

Tumour-infiltrating lymphocytes, often known as TILs, are cells that indicate the immune system is reacting to the tumour. Individuals with TIL-containing tumours usually have favourable outlooks than those without them.

Several types of Immunotherapies are used to treat cancer these include:

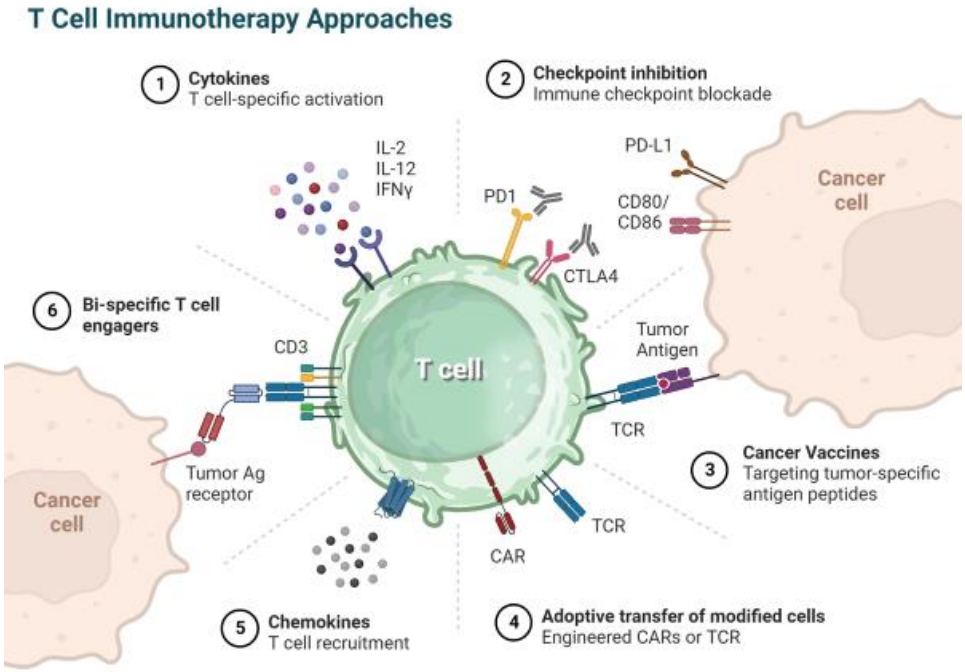
- **Immune checkpoint inhibitors**, which are drugs that block immune checkpoints. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more strongly to cancer.

- **T-cell transfer therapy**, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumour. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein. Also be called adoptive cell therapy, Adoptive immunotherapy, or immune cell therapy

- **Monoclonal antibodies**, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy.

- **Treatment vaccines**, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease

- **Immune system modulators**, which enhance the body's immune response against cancer.[1]



REVIEW MAINLY FOCUSES ON CHECKPOINT INHIBITORS

Immune checkpoints engage when proteins on the surface of immune cells called T cells recognize and bind to partner proteins on other cells, such as tumour cells. These proteins are called immune checkpoint proteins. When the checkpoint and partner proteins bind together, they send an "off" signal to the T cells. This can prevent the immune system from destroying the cancer.

Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells.

Drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1. Some tumours turn down the T cell response by producing more of PD-L1.

Checkpoint inhibitors also known as checkpoint proteins they block, such as CTLA-4 inhibitors, and PD-L1 inhibitors.

Some examples of checkpoint inhibitors include:

- Anti-CTLA-4 therapies: Ipilimumab (Yervoy) and tremelimumab
- Anti-PD-1 therapies: Cemiplimab, dostarlimab, nivolumab (OPDIVO), pembrolizumab (Keytruda), retifanlimab-dlwr, and tislelizumab
- Anti-PD-L1 therapies: Atezolizumab (Tecentriq), avelumab, and durvalumab
- Anti-LAG-3 therapy: Relatlimab

THE LIST OF ICIS WITH THE CANCER TYPE INDICATION:

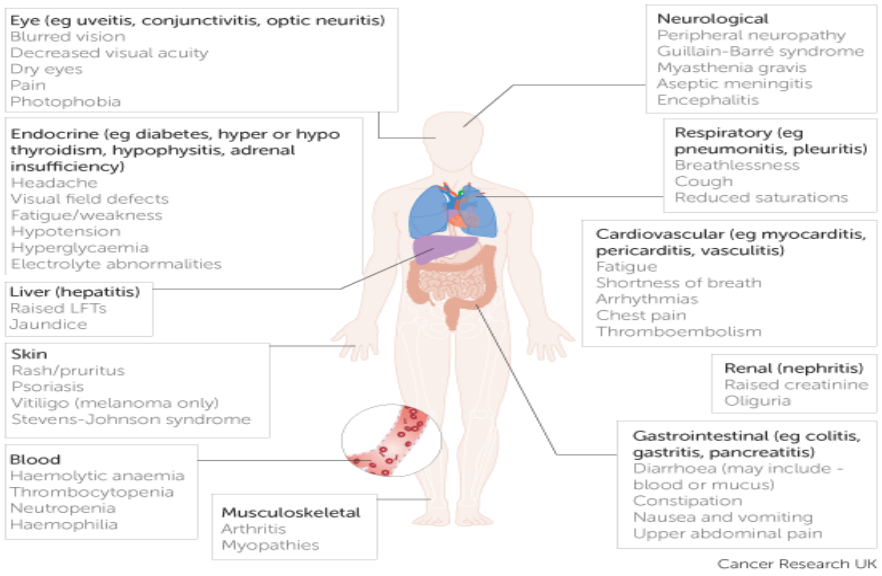
Drug	Target	Approval	FDA-Approved Indications
Nivolumab	PD-1	March 2015	MSI-H or dMMR CRC, HNSCC, HCC, melanoma, cHL, NSCLC, RCC, urothelial cancer, SCLC
Pembrolizumab	PD-1	October 2016	Cervical cancer, gastric cancer, HNSCC, HCC, cHL, melanoma, MCC, MSI-H/dMMR cancers, NSCLC, primary mediastinal DLBCL, urothelial cancer
Atezolizumab	PD-L1	October 2016	NSCLC, urothelial cancer
Cemiplimab	PD-1	September 2018	Cutaneous SCC
Ipilimumab	CTLA-4	August 2010	Melanoma, MSI-H/dMMR CRC, intermediator poor-risk RCC (in combination with nivolumab)
Avelumab	PD-L1	March 2017	MCC, urothelial cancer
Durvalumab	PD-L1	February 2016	NSCLC, urothelial carcinoma

cHL = classic Hodgkin lymphoma; CTLA-4 = cytotoxic T lymphocyte associated antigen 4; CRC = colorectal cancer; DLBCL = diffuse large B-cell lymphoma; dMMR = deficient mismatch repair; FDA = US Food and Drug Administration; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability-high; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1;
PD-L1 = programmed cell death ligand 1; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer.

Since their initial approval for the treatment of advanced melanoma, their use has expanded to the treatment of several other advanced cancer.

Unfortunately, immune checkpoint inhibitors have also been associated with the emergence of a new subset of autoimmune-like toxicities, known as immune-related adverse events. These toxicities differ depending on the agent, malignancy, and individual susceptibilities.

Although the skin and colon are most involved, any organ may be affected, including the liver, lungs, kidneys, and heart. Most of these toxicities are diagnosed by excluding other secondary infectious or inflammatory causes.



Examples of immune-related Adverse Events and some possible symptom

IMMUNE RELATED ADVERSE EVENTS (IRAES) AS PER ASCO GUIDELINES

irAE	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	Macules/papules covering <10% BSA +/− associated symptoms (e.g., pruritis, burning, tightness)	Macules/papules covering 10–30% BSA +/− associated symptoms (e.g., pruritis, burning, tightness) AND limiting ADLs	Macules/papules covering >30% BSA +/− associated symptoms (e.g., pruritis, burning, tightness) AND limiting self-care ADLs AND local superinfection	Life-threatening; SJS or widespread mucosal ulcerations (complicated rash with full-thickness dermal ulceration or necrosis)
Hypothyroidism	Asymptomatic; fT4 normal AND TSH >10 mUI/L	Moderate sx (e.g., fatigue, constipation, weight gain, loss of appetite, dry skin, eyelid edema, puffy face, hair loss); Low fT4 +/− TSH >10 mUI/L	Severe sx (e.g., bradycardia, hypotension, pericardial effusion, depression, hypoventilation, stupor, lethargy); very low fT4 and very high TSH	Life-threatening; extremely low fT4 and extremely high TSH (myxedema coma)
Hyperthyroidism	Asymptomatic; fT4 normal AND TSH suppressed (<0.3 mUI/L)	Moderate sx (e.g., weight loss, increased appetite, anxiety and irritability, muscle weakness, menstrual irregularities, fatigue, tachycardia); fT4 high AND TSH suppressed (<0.1 mUI/L)	Severe sx (e.g., arrhythmia, tremor, sweating, insomnia, diarrhea); fT4 normal AND TSH suppressed (<0.1 mUI/L)	Life-threatening; fT4 high AND TSH suppressed (<0.1 mUI/L)
Hypophysitis	Asymptomatic or mild sx (e.g., fatigue, weakness); clinical or diagnostic observations only	Moderate sx (e.g., headache, hypotension); limits IALDs	Severe or medically significant sx but not life-threatening; limiting self-care ADLs	Life-threatening consequences or any visual disturbances; urgent intervention indicated
Adrenal Insufficiency	Asymptomatic or mild sx (e.g., fatigue); clinical or diagnostic observations only	Moderate sx requiring medical intervention	Severe sx requiring hospitalization	Life-threatening adrenal crisis requiring urgent intervention (e.g., severe hypotension or hypovolemic shock, acute abdominal pain, vomiting, fever)

DERMATOLOGICAL TOXICITIES :

Dermatological toxicities are the most common reactions seen with ICIs and usually occur within the first 2 to 3 weeks after initiation of therapy been reported. The most common form of rash is a spongiotic dermatitis-like eczema described as maculopapular, faintly erythematous, and pruritic.

ENDOCRINE TOXICITIES:

Endocrine irAEs often include thyroid dysfunction, hypophysis, and, less often, primary adrenal insufficiency and type 1 diabetes mellitus. Hypothyroidism is more common than hyperthyroidism, The most serious endocrine irAEs is primary adrenal insufficiency.

GASTROINTESTINAL TOXICITIES :

Diarrhoea is defined as increased stool frequency and colitis as the presence of symptoms (e.g., abdominal pain, nausea, vomiting, fever, bloody stools These toxicities usually occur 6 to 7 weeks after therapy initiation. Initial work-up for patients with diarrhoea includes the exclusion of infectious aetiologies, such as Clostridium difficile, Salmonella, and other bacterial, parasitic, or viral causes, including cytomegalovirus.

Hepatitis tends to occur Hepatitis tends to occur within 8 to 12 weeks after initiation of therapy and usually consists of asymptomatic elevation of aspartate aminotransferase alanine aminotransferase, and bilirubin (less common) levels and fever (rarely).

PULMONARY TOXICITIES :

Pneumonitis is a potentially fatal irAEs Pulmonary and extrapulmonary sarcoidosis-like syndrome has also been described as part of the pulmonary spectrum.

RHEUMATOLOGIC TOXICITIES:

Arthralgias have been reported in patients taking ICIs. Inflammatory arthritis has been reported. Arthritis usually develops with other irAEs, occurs after 5 months of therapy, and can affect large, medium, or small joints. It may be destructive and persist after discontinuation of immunotherapy. Other rheumatoid-like toxicities include inflammatory myositis, rhabdomyolysis, giant cell arteritis, and polymyalgia-like syndrome.

NEUROLOGIC TOXICITIES:

Headache, peripheral and central nervous system symptoms may also involve. Motor or sensory peripheral neuropathies, Other peripheral toxicities include a myasthenia gravies like

syndrome, which may cause diaphragmatic involvement, and fatal Guillain-Barré-like syndrome toxicity. Central toxicities include aseptic meningitis, autoimmune encephalitis, posterior reversible encephalopathy syndrome, and transverse myelitis.

RENAL TOXICITIES:

The most common forms of nephrotoxicity include acute interstitial nephritis, lupus-like nephritis, granulomatous nephritis, diffuse interstitial nephritis, or minimal change disease toxicity include acute interstitial nephritis, Presentation varies from asymptomatic to oliguria, haematuria, and peripheral oedema

OCULAR TOXICITIES:

Ocular toxicities include conjunctivitis, episcleritis, keratitis, blepharitis, and uveitis. Uveitis may cause photophobia, blurry vision, pain, and eye dryness.

HEMATOLOGIC TOXICITIES:

Anaemia, Neutropenia, immune thrombocytopenic purpura, pure red cell aplasia, disseminated intravascular coagulopathy, and acquired haemophilia

CARDIAC TOXICITIES:

Cardiac toxicities from ICIs include myocarditis, pericarditis, arrhythmias and heart block, and new-onset heart failure[2]

irAE	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea/colitis	<4 stools/day above pt baseline	4–6 stools/day above pt baseline AND associated abdominal pain, mucus, or blood in the stool	≥7 stools/day above pt baseline AND incontinence or need for hospitalization for IV fluids ≥24 h	Life-threatening; grade 3 sx plus fever or peritoneal signs consistent with perforation or ileus
Hepatitis (these ranges may differ if the patient is receiving ICI for HCC)	AST/ALT up to 3× ULN or t-bili up to 1.5× ULN (or <2× baseline)	AST/ALT >3× ULN or t-bili >1.5–3× ULN (or >2× baseline)	AST/ALT >5–20× ULN or t-bili >3–10× ULN	AST/ALT >20× ULN or t-bili >10× ULN
Pneumonitis	Asymptomatic, diagnosis is radiographic	Sx, medical intervention is indicated as it limits IADLs	Severe sx that limit self-care ADLs; supplemental O2 is indicated	Life-threatening respiratory compromise; urgent intervention indicated
Nephritis	Serum Cr > ULN AND >1.5–2× pt baseline; 1+ proteinuria (<1 g/24 h)	Serum >2–3× pt baseline; 2+ proteinuria (<1.0–3.4 g/24 h)	Serum Cr >3× pt baseline; proteinuria >3.5 g/24 h	Life-threatening; serum Cr >6× ULN; dialysis indicated
Neurotoxicity	Asymptomatic or mildly sx	New onset moderate sx limiting IALDs	New onset severe sx (e.g., vision changes, weakness, sensory deficits); affecting self-care ADLs; not life-threatening	Life-threatening; urgent intervention indicated
Cardiotoxicity	Abnormal cardiac biomarkers or ECG	Abnormal screening tests with mild sx	Moderately abnormal testing or sx with mild activity	Life-threatening; moderate to severe decompensation, intervention required

OBJECTIVES:

Immune checkpoint inhibitors (ICIs) have significantly improved treatment for advanced malignancies, targeting checkpoints such as PD-1, PD-L1, and CTLA-4. These therapies have been approved by the FDA in various types of cancers, with response rates ranging from 15 to 30% in most solid tumours to 45-60% in melanoma and MSI-H tumours. However, a significant proportion of patients do not respond to these therapies, necessitating the identification of biomarkers to predict the most benefit from treatment. Predictive biomarker research has primarily focused on tumour signatures, but clinical biomarkers, including early-on-treatment pharmacodynamic markers, have been less studied. Immune-related adverse event (IRAE) onset may be a clinical biomarker for ICI response.

Patients experiencing IRAEs while on therapy with anti-PD-1 and anti-PD-L1 antibodies have been documented to experience improved outcomes, but this association has been less uniform in patients treated with anti-CTLA-4 antibodies. The relationship between IRAE site, severity, timing of onset, and management influences ICI effectiveness. This review will discuss seminal studies that have addressed these questions and shaped the narrative about the predictive value of IRAE onset for patients on ICIs, focusing on FDA-approved indications for ICI therapy and those involving ICIs alone.

Fatigue is a common adverse reaction (irAEs) associated with the use of Immune Checkpoint Inhibitor (ICIs), with incidence rates ranging from 16% to 71% when combined with other anticancer therapies. Fatigue is usually mild and does not interfere with daily activities. ICIs often cause dermatological toxicities within the first 2-3 weeks of therapy. Rash or pruritus is common in 50% of patients treated with anti-CTLA-4 antibodies, 40% with anti-PD-1 or anti-PD-L1 therapy, and 60% with combination therapy. Pneumonitis is a potentially fatal irAEs with an incidence of 5% in patients receiving ICIs, particularly with combination therapy and in patients with lung cancer. It occurs more often with anti–PD-1 than anti–CTLA-4 therapy, with a median time to presentation of almost 3 months.[3]

Studies have shown an association between IRAE onset and the efficacy of anti-PD-1 and anti-PD-L1 antibodies in NSCLC patients. In a retrospective study, 89.3% of patients received anti-PD-1, while 10.7% received anti-PD-L1 antibodies. Patients with IRAEs had superior progression-free survival (PFS) and overall survival (OS) compared to those without IRAEs. In a large retrospective analysis, 43.6% of patients developed IRAEs, with the most common sites being endocrine, dermatologic, and gastrointestinal toxicities. Other studies have also demonstrated similar correlations between IRAE onset and ICI efficacy. A retrospective study found that 42.2% of metastatic RCC patients treated with ICIs experienced IRAEs, with common sites being dermatologic, gastrointestinal, and endocrine. IRAEs were associated with improved overall survival and treatment. A retrospective analysis of 389 pre-treated metastatic RCC patients with nivolumab showed that 20% experienced IRAEs, with prolonged survival and a 1-year OS of 75.4 and 59.8%, respectively[4]

Common adverse events (irAEs) in cancer treatment vary based on the type of ICI treatment. Patients receiving ICI targeting CTLA-4 (53.8%) had higher incidences of irAEs than those targeting PD-1 (26.5%) or PD-L1 (17.1%). Grade 3/4 irAEs were more common with ICIs targeting CTLA-4 (31%). PD-1/PD-L1 blockade therapies, such as durvalumab, atezolizumab, and pembrolizumab, were associated with higher rates of colitis. Concurrent, dual blockade of CTLA-4 and PD-1/PD-L1 system components has increased rates of irAEs, potentially leading to treatment discontinuation. Combination therapies have shown synergistic antitumor responses and are recommended for cancer treatment.[5]

The study analysed 318 reported G ≥ 2 irAEs in 318 patients, with 229 experiencing at least one toxicity. The most common irAEs were endocrine disorders, skin toxicity, gastrointestinal toxicities, pulmonary, and hepatitis. 140 toxicities led to treatment discontinuation or temporary interruption, with 44 in LC and 96 in Mel patients. The most frequently associated regimen was the anti-CTLA4-anti-PD(L)1 combination. Gastrointestinal irAEs and hepatitis were more frequent in the Mel group, while pneumonitis and rheumatological irAEs were more frequent in LC. Thirty-six patients were challenged with a second ICI line after developing a G ≥ 2 toxicity.[6]

A study involving 517 patients with ir-fatigue data from June 2014 to April 2019 found that 74.7% of them were eligible for clinical outcomes analysis. The majority were NSCLC, melanoma, renal cell carcinoma, and other malignancies. The median age was 68 years, with 44.0% being elderly. The majority experienced grade ir-AEs, with 19.9% experiencing early ir-fatigue and 38.9% experiencing delayed ir-fatigue. 61 patients experienced both early and delayed ir-fatigue[7]

The study evaluated the incidence of colitis and diarrhea in patients with PD using single-agent ipilimumab, anti-PD-1 or anti-PD-L1, or combination therapy with ipilimumab and nivolumab. All-grade colitis occurred in 9.1% of patients with ipilimumab alone, while grade 3-4 colitis occurred in 6.8% and grade 3-4 diarrhea in 7.9%. Single-agent anti-PD-1 had lower incidences at 1.4%, 0.9%, and 1.3% for all-grade colitis, grade 3-4 colitis, and grade 3-4 diarrhea, respectively. Combination therapy with ipilimumab and nivolumab showed a higher incidence of all-grade colitis, grade 3-4 colitis, and grade 3-4 diarrhea.[8]

The incidence of cutaneous inflammatory reactions (irAEs) in patients treated with immunosuppressive drugs (ICIs) varies depending on the ICI used. Anti-CTLA-4 monotherapy has a higher incidence (44-59%) than anti-PD-1 and anti-PD-L1 monotherapy, while combination therapy with anti-PD-1 and anti-CTLA-4 agents has the highest incidence (59-72%). In severe cases, cutaneous irAEs are observed in approximately 25% of patients treated with anti-CTLA-4 agents, with 2.4% being grade 3 and 4. The prevalence of cutaneous irAEs depends on the type of cancer treated with ICIs, with MM being more likely to experience irAEs than NSCLC and RCC. Histology may affect the TME, immune infiltrate, adaptive immune response, and neoantigen formation, causing different skin toxicities.[9]

The incidence of irAEs did not significantly influence the overall survival (OS) and progression-free survival (PFS) in the entire cohort. The risk of irAEs was significantly higher with dual-agent therapy (ipilimumab/nivolumab combination) and high disease burden. The only haematological

parameter significantly different between the groups was the mean PLR, which was lower in the irAEs group. None of the thresholds for baseline haematological factors could predict the incidence of irAEs. The number of doses of ICI people who had irAEs was low compared to the non-irAEs group. Other factors such as type of primary malignancy, lung cancer, stage of the diseases at the time of ICI therapy, stage IV disease, and higher ALC seem to have a considerable association with irAEs, though the association is not statistically significant. Multivariate logistic regression showed PLT/ALC ratio as the most associated predictor in the presence of other clinical factors.[10]

CONCLUSION:

Cancer immunotherapy the Immune checkpoint inhibitors have transformed the treatment scope in various malignancies over the past two decades. Clinicians should be aware of unique toxicities Profiles. Immune checkpoint point inhibitors allow the body's innate immune system to target cancer cells by inhibiting the inhibitory signals that cancer cells transmit to T cells. Adverse effects unique to ICIs, termed as irAEs, results in immunostimulatory effect in multiple organs. While irAEs are mild, severe cases do occur can be rapidly fatal. Immunosuppressive agents initiated for the primary treatment. This extensive use had widened treatment-related and survival considerations behind creating an anti-tumour immune response to include long lasting consequences on quality of life.

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Research Article

FORMULATION AND EVALUATION OF ANTIDIABETIC HERBAL MORINGA TEA BAGS

Sakshi P. Masaye[1], Shamali S. Rane[2]
[1] Vijayrao Naik College of Pharmacy, Kankavli, Sindhudurg
[2]Asst. Professor, Vijayrao Naik College of Pharmacy, Kankavli, Sindhudurg

ABSTRACT

This report provides an overview of Moringa tea bags in the treatments of diabetes as an Antidiabetic green tea. The API used in this formulation is Moringa belonging to family Moringaceae which is commonly used to treat diabetes, skin infection, anemia, anxiety, asthma, blackheads, worms, bronchitis, and cholera. Extracts of MoringaOleifera Leaves contains antioxidants, tissue protectants, analgesic, antiulcer agents and anti-hypertensive agents. Moringa helps to decrease the elevated blood glucose levels. It also reduces insulin resistance. Hence, in this present study the Antidiabetic Tea bags have formulated using MoringaOleifera and Bitter Gourd as an Antidiabetic agent; Guduchi as an immunomodulator in the powder form. Other ingredients like Isabgol as a stool softener and Stevia sugar as sweetening agent has been used. The formulation has been evaluated by performing various evaluation test such as LOD test, water and alcohol soluble extract value, ash value, pH etc. Dipping tea bag containing the mixture of ingredients in the hot or Luke water where the extract will be formed for the administration. Dosage form shows the Antidiabetic effect in few weeks or month as it is an herbal formulation.

Antidiabetic effect in few weeks or month as it is an herbal formulation.

Keywords- MoringaOleifera, Guduchi, Bitter Gourd, Antidiabetic, Antioxidant, Asthma.

INTRODUCTION

Diabetes is a type of disease that is characterized by the increased amount of sugar in blood i.e. High blood glucose.Diabetes can be either due to the pancreas does not produce sufficient insulin or the body does not utilize the insulin in proper manner. Our body breakdowns the food into sugar i.e. glucose and it releases it into the bloodstream. When there is increase in the sugar level in the blood it's the signal for pancreas to release the insulin .This insulin helps in the producing the energy form the sugar present in the blood. More than 80% of overall population in the world is suffering from the diabetes.

Diabetes can be differentiated into main three types-

1) Type 1 diabetes
2) Type 2 diabetes
3) Gestational diabetes (diabetes occurs during pregnancy)

Symptoms of diabetes are:

1. Increased thirst
2. Frequent urination
3. Blurred vision
4. Hunger
5. Fatigue

1.1 Moringaoleifera:

Moringaoleifera, commonly known as moringa, drumstick tree, horseradish tree, bene oil tree, or benzoin tree, is the only genus in the Moringaceae family. . All parts of the moringa tree are edible and have long been consumed by humans. Moringa is commonly used to treat skin infections. , anemia, anxiety, asthma, blackheads, wounds, bronchitis, catarrh, chest congestion, cholera. It is used worldwide as a medicine. In many parts of Africa, it is commonly used for self- medication by people with diabetes, hypertension, or HIV/AIDS[1] . According to phytochemical analysis, M. oleifera is a rich source of potassium, calcium, phosphorus, iron, vitamins A and D, essential amino acids, and known antioxidants such as beta-carotene, vitamin C, and flavonoids. One of the foods that areknown

to control blood sugar levels is moringa and its leaves[3][4].

BITTER GOURD:

Momordicacharantia (*M. charantia*), also known as bitter melon, karela, balsam pear, or bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa. Its fruit has a distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd. Biochemical and animal model experiments have produced abundant data and hypotheses accounting for the anti-diabetic effects of *M. charantia*. In comparison, clinical studies with human subjects are sparse and low quality in design.

STOOL SOFTENERS:

ISABGOL: Isabgol - Isabgol also known as psyllium husk is a dietary fiber that helps to increase stool and promote laxation.Isabgol is good for weight loss as it gives a feeling of fullness and helps prevent overeating. It is also good for diabetic patients as it helps to manage blood glucose levels. Isabgol also increases the absorption of other antidiabetic drugs like metformin and enhances their glucose lowering property[11]. It is one of the most commonly used home remedies for constipation.

IMMUNOMODULATOR:

GILOY (GUDUCHI) : - Giloy, also known as Amrita or Guduchi in Hindi, that helps improve digestion and boost immunity. Giloy is Titka (bitter) in taste and Ushna (hot) in potency. Regular use of Giloy can boost energy and immunity because of its Balya (strength provider) and Rasayana (rejuvenating) qualities. The bitter taste of Giloy may help manage blood glucose levels in diabetic patients. It also increase platelet count and might help in dengue as well as in the fever condition. Giloy powder, Kadha (tea) or tablets can also br used for various skin problems as it helps to remove toxins from the body. You can apply Giloy leaf paste on the skin to fasten the wound healing[12].

SWEETNER:

STEVIA: The leaves contain a number of sweet-tasting chemicals known as steviol glycosides, which can be used fresh or dried to sweeten beverages or desserts and can be commercially processed into powdered noncaloric sweeteners. Steviol glycosides, particularly the chemicals stevioside and rebaudioside A, can be more than 300 times sweeter than table sugar and are nonglycemic (i.e., they do not affect blood glucose levels) [13]. All this ingredients were used to prepare the anti diabetic tea bag, were Moringa is used as the main constituent. While giloy is used as a immunomodulator and isabgaol is used as the stool softener .Other anti diabetic agent used is Bitter gourd which also helps in reducing the blood glucose. Stevia is used as a sweetener.

Material and Equipment:

Ingredients used in formulation areas follows:

INGREDIENTS	QUNATITY TAKEN	USES
Moringa Olifera(powder)	3-4gm	Anti diabetic Anti inflammatory
Bitter gourd (powder)	1.5-2.5gm	Anti diabetic Weight loss
Guduchi (powder)	0.20-0.30gm	Immunomodulator Anti diabetic
Isabgol (powder)	Q.S	Stool softner
Stevia (sugar)	Q.S	Sweetening agent

METHODOLOGY IDENTIFIED:

1) Collect all the required ingredients from the local distributor.
2) Ingreients were seperately seived using the sieve of the mesh size 80.
3) All the ingredeints were properly weighed using electrical weighing balance.
4) All the sieve ingredients are mixed together.
5) Powder characteristics of formulation was evaluated.
6) Then the powder formulation was filled in the cotton tea bag.
7) Further evaluation of tea bags was done by using evaluation of tea bags.

Evaluation Parameter:

1) Loss on drying (LOD TEST): Weigh the empty petridish take 2gm of powder sample into it place this petridish in hot air oven for 1hr and calculate weight of petridish frequently. Repeat this procedure until the weight of petridish becomes equal note down constant reading of loss on drying of herbal formulation.

2) Water soluble exttract value:
Take 5mg of powder sample of herbal drug in a conical flask add 90ml of water and add 10ml of chloroform keep it for magnetic stirring for 6 hours then place it for 18 hours filter it and take 25ml of filtrate from that evaporate it.

3) Alcohol soluble extractive value:
Take 5mg of powder sample of herbal drug mixture in a conical flask add 100ml of alcohol into it keep it for magnetic stirring for 6 hours then place it for 18 hours filter it and take 25ml of filtrate form that evaporate it.

4) Ash value:
Weight the empty crucible add 2gm of herbal formulation weigh the crucible place the crucible in a muffle furnace at 1000 degree Celsius. The sample is allow to cool and calculate the weight of crucible subtract the weight of crucible with powder Ash from empty weight of crucible.

5) pH=5.4:
Take few grams of sample in a beaker add few ml of water in it calculate pH of sample by using pH meter or pH paper.

6) Bulk density:

Bulk density is defined as the mass of powder divided by bulk volume. The bulk density of powder depends upon particles size distribution, particle shape, and the nature of particle to adhere to each other .

LBD =WEIGHT OF POWDER/VOLUME OF PACKING

TBD = WEIGHT OF POWDER/TAPPED VOLUME OF A PACKING

7) Tapped Density: Is is calculated by tapping bulk volume of powder for 15min.

Tapped density = Weight of sample/tapped volume

ASSAY OF AMYLASE ENZYME BY COLORIMETRY:

Solubility testing was done of the formulation using distilled water, DMSO (*Di Methyl Sulf Oxide*) and 20% alcohol. Since, the formulation was not completely soluble it was filtered and extract was separated by using the various volumes and concentrations:

% of formulation	Distilled water(10ml)	DMSO(10ml)
0.1% (0.01gm)	10ml	10ml
0.5% (0.05gm)	10ml	10ml
1.0% (0.1gm)	10ml	10ml

Further tests to get standard graph was done, in which 6 test tubes were prepare:

1 .Glucose which is the product of amylase was used to prepare the standard graph, which will help us to know the enzyme activity of the extract that was extracted from the formulation.

2. This will show us how much our formulation will perform its activity.

3. To perform this tests, Sample tubes were taken and then given quantity of Glucose, Distilled water, and DNSA (*Di nitro salicylic Acid*) were added to each sample tubes and then kept in water bath for 10min. until the color of solution becomes darker to its original color.

4.Then Colorimeter was used to get the readings of the samples tubes.

Final readings after examining all the test tubes through the colorimeter

Concentration(200µg/ml)	Absorbance
Blank	-
200	0.01
400	0.06
600	0.07
800	0.10
1000	0.13

5. Further substrate is prepared, which contains 1% Starch.

6. Then 2.5gm of amylase is mixed with 50ml of distilled water and enzyme solution is prepared.

7. Then take 5 test tubes and in each test tube Substrate, Enzyme and Inhibitor is added according to the given quantity. Then the test tubes are kept at the optimal temperature in incubator for 30min. at 37°C.

8. After incubation 1ml DNSA was added in each test tubes and then kept in water bath up to 10min.

9. After cooling the test tubes add 6ml of Distilled water to each test tube to make up the volume up to 10ml, before taking the reading on the colorimeter.

10. Then the intensity is measured at 530nm. On colorimeter.

Observation table

Test tubes	Readings
Test tube 1	0.01
Test tube 2	0.03
Test tube 3	0.01
Test tube 4	0.02

6. RESULT & DISCUSSION

The herbal tea bags prepared shows the extraction in the hot or Luke hot water. It can be use in treatment of diabetic as a anti diabetic green tea. The dosage form (tea bag containing anti diabetic drug) was prepared and evaluated. The drug having the anti diabetic effects were used for preparation of tea bags. The dosage form shows the effects in few week or month as it is herbal formulation.

Other required parameter like Water soluble extractive index, Alcohol soluble extractive index, Tapped density, Bulk density, Ash value, Loss on drying, pH, etc ere studied and also assay of alpha amylase for it's antidiabetic activity found to be in prescribed range.

As the diabetic condition and the patients after the Covid pandemic increased at all the ages of people .Considering that this formulation was decided to be prepared so that the patient can receive the cure without consuming the allopathic medicine that cause allergic condition in some patients . So to ensure that patient receives the proper dose of medicine in the daily routine with any side effect this Moringa anti diabetic tea bags were prepared. Firstly the selection of the ingredients was done and after that there evaluation testes were performed. After doing the various evaluation tests and assay of alpha amylase which showing antidiabetic activity were performed and the herbal moringa antidiabetic tea bag was prepared.

As most of the people are growing towards the Ayurvedic medicine this can be the best option for the diabetic patients to replace the normal tea with this tea so that they will be able to see the effect after few weeks or months.

So this can also be use as a best alternative for the diabetic patients and can help in boosting the immunity of the patients.

CONCLUSION

The dosage form (tea bag containing anti diabetic drug) was prepared and evaluated. The drug having the anti diabetic effects were used for preparation of tea bags. The dosage form shows the effects in few week or month as it is herbal formulation. Other required parameter like Water soluble extractive index, Alcohol soluble extractive index, Tapped density, Bulk density, Ash value, Loss on drying, pH, etc ere studied and assay of alpha amylase for it's antidiabetic activity found to be in prescribed range.

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Review Article

HER2 Positive and Triple Negative Breast Cancer: A Review

Viola Vinita DSA[1*], Amith M N[1], Umesh M[2], Charan C S[3], Hanumanthachar Joshi[4]
[1]5th PharmD, Sarada Vilas College of Pharmacy, Mysuru
[2]Associate Professor, Department of Pharmacy Practice, SVCP, Mysuru
[3]Head, Department of Pharmacy Practice, SVCP, Mysuru
[4]Principal, Sarada Vilas College of Pharmacy, Mysuru
Corresponding Author: Viola Vinita DSA, Email: violavinitad@gmail.com

ABSTRACT:

Background: Cancer is the most common cause of mortality and morbidity seen in all over the world. Breast cancer is the second most prevalent type of non-skin cancer and the fifth most common cause of cancer-related mortality worldwide, accounting for 10.4% of all cancer incidences among women. HER2 is a protein that plays a role in cell growth and differentiation accounts for 15-20% of HER2-Positive breast cancer. Lack of expression of Estrogen & Progesterone Receptor and the absence of human epidermal growth factor receptor 2 (HER2) and accounts for 15% of Triple negative breast cancer of all cases.

Objectives: Improving the prognosis of overall survival and disease-free survival of HER2-Positive and Triple Negative Breast Cancer. Reducing the risk of recurrence through effective adjuvant chemotherapy. Balancing the treatment efficacy with minimal side effects and improving overall quality of life.

Methods: Relevant articles from various journals were analyzed and reviewed.

Conclusion: Advanced targeted therapies have improved the treatment and prognosis of HER2-Positive and Triple Negative Breast Cancer.

Keywords: Breast Cancer, HER2 Positive, TNBC, Chemotherapy, NACT

INTRODUCTION:

The World Health Organization (WHO) defines "breast cancer" as malignancies that arise in the breast tissue, typically from the inner lining of the ducts or the lobules supplying to the milk ducts. Breast cancer is the second most prevalent type of non-skin cancer (after lung cancer) and the fifth most common cause of cancer-related mortality worldwide, accounting for 10.4% of all cancer incidences among women. 5,19,000 fatalities globally from breast cancer in 2004 (7% of all deaths; nearly 1% of all deaths) were attributed to the disease. Women are almost 100 times more likely than men to develop breast cancer, but men typically have worse results because of delayed diagnosis. The glandular tissues and the stromal (supporting) tissues are the two primary tissue types that make up the breast. The lobules, or milk-producing glands, and the ducts, or milk tubes, are located in the glandular tissues, whereas the stromal tissues are the fatty and fibrous connective tissues of the breast. Additionally, lymphatic and immune system tissue that eliminates waste products and cellular fluids makes up the breast [1].

Types of Breast Cancer:

1. **Non-Invasive Breast Cancer** cells that remain inside the ducts and do not spread to the breast's surrounding fatty and connective tissues. The most frequent non-invasive breast cancer kind, accounting for 90% of cases, is ductal carcinoma in situ (DCIS). Less frequently occurring lobular carcinoma in situ (LCIS) is thought to be a sign of an elevated risk of breast cancer.

2. **Invasive Breast cancer** cells that spread to the surrounding fatty and connective tissues of the breast after breaching the duct and lobular wall.

Causes of Breast Cancer:

- Genetic Factors
- Significant Family History
- Hormonal Causes
- Lifestyle and Dietary Cause

Signs and Symptoms:

- A lump in the breast or underarm is the typical sign of breast cancer. Being familiar with the texture, size, cyclical variations and skin condition of your breasts can be achieved by performing monthly breast self-examinations (BSEs).
- Breast cancer is generally indicated by symptoms like breast swelling or lump (mass), swelling in the armpit (lymph nodes), clear or bloody nipple discharge, nipple pain, inverted

(retracted) nipple, scaly or pitted skin on nipple, persistent breast tenderness, and unusual breast pain or discomfort.

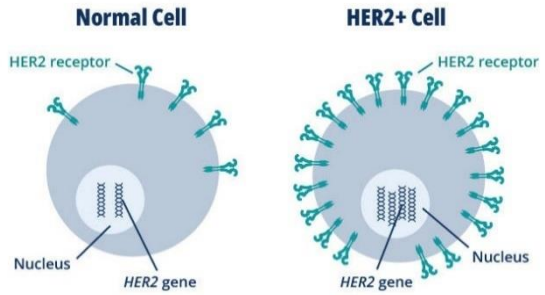
Diagnosis & Management:

Breast cancer is usually diagnosed by biopsy of nodule detected by mammogram or by PET-CT scan. Chemotherapy (Neoadjuvant & Adjuvant), Radiation Therapy, Surgery (Breast Conserving surgery – Lumpectomy, Quadrantectomy & Mastectomy) are the treatment [1].

HER 2 Positive Breast Cancer:

HER2 stands for human epidermal growth factor receptor 2, a protein that plays a role in cell growth and differentiation. Normally, HER2 receptors help to control the growth and repair of breast cells.

However, when the HER2 gene mutates, it can lead to an overproduction of the HER2 protein. The receptor tyrosine-protein kinase erbB-2 known as Human Epidermal Growth Factor Receptor 2 (HER 2) is typically involved in the proliferation of breast cells that are called as HER2- Positive Breast Cancer. Approximately 15-20% of breast cancers are HER2-Positive breast cancer [2].

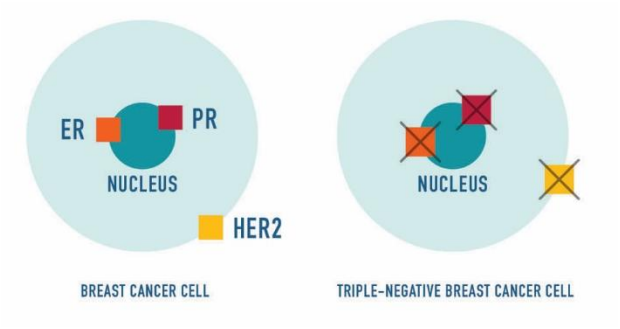


(Fig. 1) HER2 Gene Amplification / protein overexpression

Triple Negative Breast Cancer (TNBC):

TNBC can account for up to 15% of all cases. TNBC is defined by the lack of expression of the estrogen receptor (ER), the progesterone receptor (PR) and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or gene amplification.

According to the guidelines of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP), ER and PR are considered negative when <1% of tumor cells show nuclear staining via immunohistochemistry. It is more common in younger women and women with a BRCA1 gene mutation. [3]



(Fig. 2) Breast cancer cells typically have some combination of the estrogen receptor (ER), progesterone receptor (PR), and overexpressed HER2. But triple-negative breast cancer (TNBC) cells lack all three of these.

Objectives of HER2-Positive and Triple Negative Breast Cancer:

- Improving the prognosis of overall survival and disease-free survival of HER2-Positive and Triple Negative Breast Cancer.
- Reducing the risk of recurrence through effective adjuvant chemotherapy (post-surgery treatment).
- Balance treatment efficacy with minimizing side effects & improving patients' quality of life[2,3].

Diagnostic Test in HER2- Positive Breast Cancer:

Immunohistochemistry (IHC): Measures the amount of HER2 protein on the surface of cells. Results are scored from 0 to 3+, with 3+ indicating HER2-positivity [4].

❖ Immunohistochemistry (IHC) for HER2 Positive sensitivity testing:

IHC Score	HER 2-test amplification	HER2 status
0	No staining or incomplete and faint/barely perceptible membrane staining n < 10% of tumor cells	Negative
1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low **NO** ⬆
2+	Weak-moderate complete membrane staining in >10% of tumor cells or intense membrane staining n<10% of tumor cells	FISH amplification **YES** ⬇
3+	Complete and intense membrane staining in >10% of tumor cells	Positive

❖ Fluorescence In Situ Hybridization (FISH): Measures the number of copies of the HER2 gene within the cancer cells. It provides a positive or negative result [5].

Status	Score	Significance	Reflex HER2 FISH
Positive	3+	Uniform intense membrane staining of >30% tumor cells	No
Equivocal	2+	Complete membrane staining, non-uniform or weak in intensity, in at least 10% of the cells or intense complete membrane staining in 30% or less of tumor cells	Yes
Negative	1+	Weak or incomplete membrane staining in any population of tumor cells	No
Negative	0	No staining	No

Diagnostic Tests in Triple Negative Breast Cancer:

Immunohistochemistry in Triple Negative Breast Cancer (TNBC):

- Estrogen Receptor (ER) Negative: The cancer cells do not have receptors for estrogen.
- Progesterone Receptor (PR) Negative: The cancer cells do not have receptors for progesterone.
- HER2 Negative: The cancer cells do not overexpress the HER2 protein [6].

IHC Markers

- ER and PR: Antibodies against ER and PR are used to detect the presence of these hormone receptors.
- HER2: Anti-HER2 antibodies are used.
- Ki-67: Antibodies against the Ki-67 protein, a marker of proliferation, are used.
- Androgen Receptor (AR): Antibodies against the androgen receptor are use [6].

Grading:

HER2-Positive breast cancer [7]

Grade 1 (Low grade)	Well differentiated cells that look more like normal cells
Grade 2 (Intermediate grade)	Moderately differentiated
Grade 3 (High Grade)	Poorly differentiated cells that look very different from normal cells.

Triple Negative Breast Cancer [8]

Grade 1 (Low grade)	Rare in TNBC
Grade 2 (Intermediate grade)	Less Common
Grade 3 (High Grade)	Most TNBC cases are grade 3, aggressive type

BI-RADS CATEGORY:

The Breast Imaging Reporting and Data System (BI-RADS) is a standardized system used for interpreting and reporting mammography, ultrasound, and MRI results of breast imaging. Developed by the American College of Radiology (ACR), BI-RADS helps radiologists communicate findings consistently and clearly, aiding in management decisions. The BI-RADS system includes categories ranging from 0 to 6 [10].

BI-RADS 0: Incomplete

Additional imaging evaluation and/or prior mammograms for comparison are needed.

BI-RADS 1: Negative

No significant findings.

BI-RADS 2: Benign Finding

Non-cancerous findings such as cysts or fibroadenomas.

BI-RADS 3: Probably Benign

Findings have a high probability (≥ 98%) of being benign.

BI-RADS 4: Suspicious Abnormality

Findings that do not have the classic appearance of cancer but have a reasonable probability (2-95%) of being malignant

Subcategories:

4A: Low suspicion for malignancy (2-10%).

4B: Moderate suspicion for malignancy (10-50%).

4C: High suspicion for malignancy (50-95%).

Management: Tissue diagnosis (e.g., biopsy).

BI-RADS 5: Highly Suggestive of Malignancy

Findings have a high probability (≥ 95%) of being cancer.

BI-RADS 6: Known Biopsy-Proven Malignancy

Lesions already confirmed as cancer through biopsy [10].

STAGING: Staging determines the extent of cancer spread and is based on the TNM system (Tumor size, Node involvement, Metastasis) [9]

Adjuvant Chemotherapy:

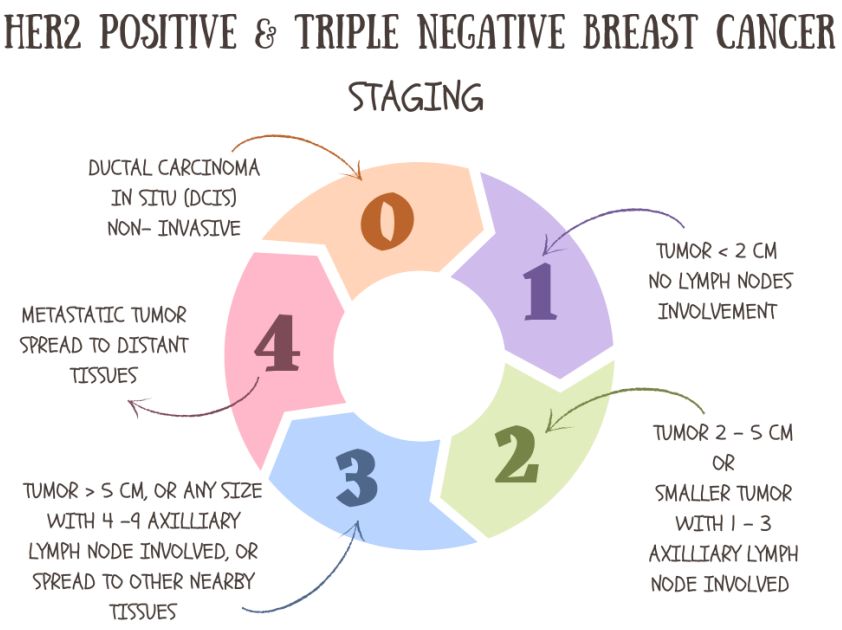
It has been shown that adjuvant chemotherapy is beneficial for survival when used to eradicate occult distant metastases that were already present at the time of surgery [11].

Neoadjuvant Chemotherapy treatment for HER2-Positive Breast Cancer:

❖ **TCH Regimen: (Docetaxel+ Carboplatin+ Trastuzumab)**

"TCH" is a chemotherapy regimen commonly used in the treatment of breast cancer. The acronym stands for,

- **T**: Docetaxel (Taxotere)
- **C**: Carboplatin
- **H**: Trastuzumab (Herceptin)



Management of HER2-Positive and Triple Negative Breast Cancer:

Neoadjuvant Chemotherapy (NACT):

The term neoadjuvant chemotherapy (NACT) is used to describe chemotherapy given before locoregional therapy. Despite the prefix 'neo' from Greek meaning 'new' with the adjective 'adjuvant' from Latin meaning 'assistant', such treatment is not new; it was shown to be effective therapy. The aim of NACT was to achieve prompt tumour shrinkage thus facilitating subsequent radical mastectomy or radiotherapy.

Indications:

The TCH regimen is used for patients with HER2-positive breast cancer. HER2 (human epidermal growth factor receptor 2) is a protein that can promote the growth of cancer cells. In about one of every five breast cancers, the cancer cells have a gene mutation that makes an excess of the HER2 protein.

Administration:

The TCH regimen is typically administered in cycles, with each cycle lasting 21 days. The number of cycles can vary depending on the patient's

specific condition and response to treatment, but a common approach involves six cycles.

Side Effects:

Like all chemotherapy regimens, TCH can cause side effects. These may include:

- Fatigue
- Nausea and vomiting
- Hair loss
- Neutropenia (low white blood cell count)
- Anaemia (low red blood cell count)
- Increased risk of infection
- Peripheral neuropathy (numbness and tingling in the hands and feet)
- Cardiotoxicity (heart-related side effects, particularly with trastuzumab)

Monitoring and Support:

Patients on the TCH regimen require regular monitoring to manage side effects and to assess their response to treatment. This often involves:

- Blood tests to monitor blood cell counts and organ function.
- Heart function tests, especially with the use of trastuzumab.
- Supportive medications to manage side effects, such as anti-nausea drugs and growth factors to boost white blood cell counts.

The other treatment options involved in treating HER2-Positive Breast Cancer are:

❖ AC Regimen (Adriamycin + Cyclophosphamide) – 4 cycles – Each cycle lasts 21 days.
❖ Weekly Paclitaxel – 12 cycles
❖ TC Regimen (Docetaxel + Cyclophosphamide) – 4 cycles – Each cycle lasts 21 days.

Neoadjuvant Chemotherapy for Triple Negative Breast Cancer:

Anthracyclines (Adriamycin) & Taxanes (Paclitaxel) are used in the treatment of Triple Negative Breast Cancer.

❖ **Anthracycline(e.g., Doxorubicin/Adriamycin)**

❖ **Doxorubicin (Adriamycin)** is a type of anthracycline that works by intercalating DNA, inhibiting topoisomerase II, and generating free radicals, leading to DNA damage and cell death.

Regimen involving Doxorubicin:

- Often used in combination with cyclophosphamide (AC regimen).
- Administered intravenously.

Side Effects:

- Cardiotoxicity (potential heart damage), requiring monitoring of heart function.
- Myelosuppression (decreased bone marrow activity leading to lower blood cell counts).
- Nausea and vomiting.
- Hair loss.
- Risk of secondary cancers (though rare).

❖**Taxanes (e.g., Paclitaxel/Taxol)**

Paclitaxel (Taxol) is a type of taxane that stabilizes microtubules and prevents their disassembly, thereby inhibiting cell division and leading to cell death.

Regimen involving Paclitaxel:

- Often used after the administration of anthracyclines (sequential therapy) or in combination (concurrent therapy).
- Administered intravenously, typically weekly or every three weeks.

Side Effects:

- Peripheral neuropathy (numbness and tingling in the hands and feet)
- Myelosuppression
- Allergic reactions (premedication with steroids and antihistamines is common)
- Hair loss
- Fatigue

Monitoring parameters: Cardiac monitoring, neuropathy, blood tests and supportive care[12].

Surgery: Surgery is the primary breast cancer treatment. Breast cancer surgeries include:

➢ **Mastectomy: A mastectomy is a surgical procedure** to remove one or both breasts, partially or completely. It's often used to treat breast cancer or reduce the risk of developing breast cancer.

Types of Mastectomies:

1. Total (Simple) Mastectomy
2. Modified Radical Mastectomy
3. Radical Mastectomy
4. Skin-Sparing Mastectomy

5. Nipple-Sparing Mastectomy

Potential Complications:

- Infection.
- Bleeding or hematoma formation.
- Seroma (fluid buildup under the skin).
- Lymphedema (swelling due to lymph node removal).
- Pain or changes in sensation in the chest or arm.
- Complications related to reconstruction if performed [13].

➢ **Lumpectomy:** A lumpectomy, also known as breast-conserving surgery, is a surgical procedure to remove a breast tumour (lump) and a small margin of surrounding healthy tissue. It's often used to treat early-stage breast cancer, aiming to conserve as much of the breast as possible.

Indications for Lumpectomy:

1. **Early-Stage Breast Cancer**
2. **Ductal Carcinoma In-Situ (DCIS)**

Potential Complications:

- Infection.
- Bleeding or hematoma formation.
- Seroma (fluid buildup under the skin).
- Changes in breast shape or appearance.
- Pain or tenderness in the breast or underarm area.
- Lymphedema (if lymph nodes are removed) [14].

➢ **Breast Reconstruction:** Breast reconstruction is a surgical procedure to restore the shape of the breast after a mastectomy or lumpectomy. The goal is to create a breast that is similar in shape, size, and appearance to the natural breast [15].

Adjuvant Chemotherapy for HER2-Positive and Triple Negative Breast Cancer:

AC-T Regimen:

The AC-T regimen is a combination chemotherapy treatment often used in the management of certain types of cancer, particularly breast cancer. This regimen includes the following drugs:

1. **Adriamycin (Doxorubicin)**
2. **Cyclophosphamide**
3. **Taxanes (Paclitaxel or Docetaxel)**

Side Effects:

Common side effects of the AC-T regimen can include:

- Nausea and vomiting
- Hair loss
- Fatigue
- Increased risk of infections (due to lowered white blood cell counts)
- Mouth sores
- Neuropathy (nerve damage causing numbness and tingling, more common with Taxanes)

Monitoring and Supportive Care:

Patients undergoing the AC-T regimen typically require close monitoring, including regular blood tests to check blood counts, liver and kidney function, and cardiac function (due to the potential cardiotoxicity of Adriamycin). Supportive care measures, such as anti-nausea medications and growth factors to boost white blood cell counts, are often used to help manage side effects [12].

Pertuzumab +Trastuzumab + Docetaxel:

The combination of Pertuzumab, Trastuzumab, and Docetaxel is a commonly used regimen for the treatment of HER2-positive breast cancer.

Indications:

This regimen is typically used for:

- Neoadjuvant treatment (before surgery) in HER2-positive, locally advanced, inflammatory, or early-stage breast cancer.
- Adjuvant treatment (after surgery) in HER2-positive breast cancer.
- First-line treatment for HER2-positive metastatic breast cancer.

Common Side Effects:

- **Pertuzumab and Trastuzumab**
  - Diarrhoea
  - Infusion-related reactions (fever, chills, rash)
  - Cardiotoxicity (heart problems, including decreased heart function)

- **Docetaxel**:

- Neutropenia (low white blood cell counts)
- Fatigue
- Hair loss
- Neuropathy (nerve damage causing numbness and tingling)

- Nail changes

Monitoring and Supportive Care:

Patients receiving this regimen require regular monitoring, including:

- Cardiac function tests (e.g., echocardiograms or MUGA scans) due to the potential cardiotoxicity of pertuzumab and trastuzumab.
- Blood tests to monitor for neutropenia and other side effects.
- Supportive medications to manage side effects, such as anti-nausea drugs, growth factors to boost white blood cell counts, and medications to manage diarrhoea [12].

Importance of Neoadjuvant Therapy in HER2-Positive Breast Cancer

1. **Tumour Shrinkage:** Neoadjuvant therapy can significantly shrink tumours, making them operable and allowing for less extensive surgery, potentially conserving more breast tissue.
2. **Assessment of Treatment Response:** It provides an opportunity to assess the tumour's response to therapy.
3. **Early Systemic Treatment:** Administering systemic therapy early can target micro metastatic disease, potentially improving long-term outcomes.
4. **Personalized Treatment**: The response to neoadjuvant therapy can help tailor postoperative (adjuvant) treatment.

Importance of Neoadjuvant Therapy in Triple-Negative Breast Cancer (TNBC)

1. **Tumour Reduction:** Similar to HER2-positive cancers, neoadjuvant therapy can reduce tumour size, making surgery easier and potentially less invasive.
2. **Prognostic Information:** The response to neoadjuvant chemotherapy in TNBC can be a strong predictor of long-term outcomes.
3. **Early Intervention:** TNBC is an aggressive subtype, and early systemic treatment can help control the disease and address micro metastatic spread.

Drawbacks and Limitations of Neoadjuvant Chemotherapy in HER2-Positive and Triple Negative Breast Cancer:

- Toxicity and Side effects
- Delayed surgery leads to the progression of disease
- Clinical and molecular subtypes
- Cost efficacy [16]

Future Directions:

Clinical trials and ongoing research are key to enhancing the prognosis for patients with TNBC and HER2-positive status. Priorities for treating HER2-positive breast cancer include creating new targeted therapies and comprehending resistance mechanisms. Finding new targets for therapy for TNBC, enhancing specific treatment plans, and perfecting immunotherapy techniques [17].

Conclusion:

HER2-positive and triple-negative breast cancer (TNBC) are two aggressive subtypes of breast cancer that present unique challenges and opportunities in treatment and management. Neoadjuvant therapy has dramatically improved the prognosis for HER2 Positive & TNBC Patients by enhancing survival rate and reducing recurrence. Neoadjuvant therapy, which includes HER2-Targeted agents combined with chemotherapy, has been particularly effective in shrinking tumours pre-operatively and improving surgical outcomes. Recent advancements in immunotherapy provides hope for improved treatment options.

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INTERNATIONAL JOURNAL OF COMMUNITY PHARMACY
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International Journal of Community Pharmacy

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- To organize into an association of all persons engaged in, interested in or connected with community pharmacy.
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- To develop and promote standards of education and training for community pharmacy.
- To develop and promote short term informal training programs for individuals interested in community pharmacy.
- To educate hospital trustees, Board of Directors, Board of Visitors and the public to understand that the practice of community pharmacy calls for special training and experience.
- To serve as a forum for exchange of ideas and experiences, and collection and dissemination of information in general community pharmacy.
- To spread the knowledge on the principles, practices, techniques and methods concerning community pharmacy.
- To promote and safeguard the status and the interest of community pharmacy and the interests of those engaged in it.
- To promote sponsor, submit, memorandums, petitions and representations to local, state, union and other authorities for better laws, and influence legislation which affect hospitals and other community pharmacy organizations.
- To organize conferences, seminars, meetings and discussions for the promotion and furtherance of the aims and objects of the ACPI.
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The official publication of Association of Community Pharmacists of India (ACPI)
Secretariat & Communication address
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Ph : 0821-4262415