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Editorial

Greetings from IJCP

As we navigate the ever-evolving landscape of pharmaceutical sciences, it is with great pleasure that I extend my warmest greetings to you in this edition of the International Journal of Community Pharmacy. Our commitment to advancing knowledge in pharmacy resonates strongly, and the array of research articles within these pages exemplifies the dedication and innovation thriving in the global community of pharmaceutical researchers.

1. Bridging the Gaps: Patient-Centric Approaches

The cornerstone of community pharmacy lies in its direct impact on patient care. In this issue, we explore groundbreaking studies elucidating patient-centric approaches that bridge the gaps between healthcare providers and individuals. From medication adherence interventions to the integration of digital health tools, the articles featured underscore the pivotal role community pharmacists play in enhancing overall health outcomes.

2. Pharmacological Frontiers: Unveiling Novel Therapeutics

Our journal proudly showcases the forefront of pharmacological research, unveiling novel therapeutics that have the potential to redefine treatment paradigms. Whether it be the discovery of new drug entities, exploration of innovative delivery systems, or the optimization of existing medications, the articles within this section provide a panoramic view of the diverse and dynamic nature of pharmaceutical research.

3. Community Pharmacy Practice: Innovations and Challenges

The practice of community pharmacy is not static; it evolves with the needs of the community it serves. Delve into this issue to explore the latest innovations and challenges in community pharmacy practice. From the implementation of advanced pharmaceutical services to navigating regulatory landscapes, our authors shed light on the multifaceted dimensions that shape the day-to-day operations of community pharmacies worldwide.

4. Global Collaborations: Driving Impactful Research

Research knows no borders, and in this edition, we highlight the significance of global collaborations in driving impactful research. The collaborative efforts showcased in these pages underscore the power of diverse perspectives and cross-cultural exchanges, enriching the discourse surrounding community pharmacy on a global scale.

As the editor, I express my sincere gratitude to the dedicated authors, esteemed reviewers, and the tireless editorial team for their unwavering commitment to excellence. Together, we continue to weave the tapestry of knowledge that propels the field of community pharmacy forward.

I invite you to immerse yourself in the wealth of insights and discoveries presented in this issue. May it inspire new ideas, spark collaborations, and contribute to the collective pursuit of advancing pharmaceutical science for the betterment of communities worldwide.

Warm regards,

Dr. Hanumanthachar Joshi
Editor-in-Chief
International Journal of Community Pharmacy

Review Article

PHARMACOGNOSTIC PROFILE AND PHARMACOLOGICAL ACTIONS OF *Helicteres isora* Linn: A REVIEW

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ABSTRACT:

The single use of herbal medicines, or in combination with other therapies are a prominent choice of many people as they can demonstrate advantages over chemotherapy or radiotherapy such as the reduction of side effects and efficiency for long term use. The development of many current medicines for the treatment of various diseases such as inflammation, diabetes, or cancer is primarily based on natural sources, including herbal plants. *Helicteres isora* Linn has been used traditionally as a folk medicine for treatment of various common diseases such as colic, constipation, diabetes, gastropathy, scabies, diarrhea, dysentery, snake bite, dog bite and inflammation. As a potential medicinal plant, many attempts have been made to identify the key bioactive compounds in *H. isora* and conduct in-vitro and in-vivo tests to investigate their potential as therapeutic agents for various diseases. 80% of world's population relies on traditional medicines and plant extracts and the active constituents are used to meets people's primary healthcare needs. This review focuses on compilation of pharmacognostic profile and pharmacological actions of *Helicteres isora* Linn plant.

Key wards: Ayurveda, *Helicteres isora*, Pharmacological actions, Phytoconstituents.

INTRODUCTION:

Helicteres isora Linn. (*H. isora*) is a large genus of tropical trees and shrubs belongs to family Sterculiaceae, with axillary flowers and fruits consisting of five twisted carpels. The origin of *H. isora is* new Latin, from Greek *heliktēres*, plural of *heliktēr* anything twisted, from *helik-*, *helix* spiral [1]. *H. isora* is a shrub or small tree belongs to family Sterculiaceae. It spreads rapidly with stem measuring 1-5 inches in diameter, reaching a height of 5-15 feet. This species is native to Asia and Australia [2]. It is commonly known as Marodphali, Marorphali, Enthani, etc. due to the screw-like appearance of its fruit. It is not described broadly in the ancient text of Ayurveda, namely Samhitas and Nighanthu. This plant can come from outside so it is neglected by Ayurvedic authors. In the description from the Ayurvedic plant Murva, Avartphala is also confusing with Murva, but later confirmed with a separate plant instead of Murva. Avartphala leaf resembles Parushaka (Grewia Asian Linn) [3].

Pharmacognostic profile of *Helicteres isora* Linn.

Botanical name: *Helicteres isora* Linn.

Scientific Synonyms [4]: The various scientific synonyms of *H. isora* are enlisted in Table 1.

Table 1: Scientific synonyms of *H. isora*

Sr. No.	Scientific synonyms
1	Helicteres chrysocalyx Miq. ex Mast.
2	Helicteres corylifolia Buch.-Ham. ex Dillwyn
3	Helicteres grewiaefolia DC.
4	Helicteres isora var. glabrescens Mast.
5	Helicteres isora var. microphylla Hassk.
6	Helicteres isora var. tomentosa Mast.
7	Helicteres macrophylla Wight ex Wight & Arnold
8	Helicteres ovata var. fructus-regis Lam.
9	Helicteres ovata var. isora-murri Lam.
10	Helicteres roxburghii G. Don
11	Helicteres versicolor Hassk.
12	Isora corylifolia Schott & Endl.
13	Isora grewiaefolia (DC.) Schott & Endl.
14	Isora versicolor Hassk.
15	Ixora versicolor Hassk.

Common names

It is commonly known as Indian screw tree, East Indian screw tree, Deer's horn in English, Avartani, Avartaphala in Sanskrit, Marodphali, Marorphali, Enthani, Gomathi in Hindi, Kewad, Muradsheng in Marathi, Antamora in Bengali, Maradashingh in Gujrati, Yedmuri in Kannada, Valampuri in Telgu, Idampiri valampiri in Malayalam, S̄amunpra pai ka bid in Thai, Liniya in Sinhala, Muemuriya in Oriya, etc [3, 5].

Other vernacular names include mochra, mudmudika, kurkurbicha, sinkri, valumbari, yedamuri, pita baranda, balampari, guvadarra, pedamuri, ishwarmuri, murmuriya, and vurkatee. In Indonesia it is called buah kayu ules or ulet-ulet on Java [5, 6].

The scientific classification of *H. isora* is shown in Table 2

Kingdom	**Plantae**
Clade	Tracheophytes
Clade	Angiosperms
Clade	Eudicots
Clade	Rosids
Order	Malvales
Family	Malvaceae
Genus	Helicteres
Species	*H. isora*

Geographical Distribution

H. isora is a tropical Asian plant. It is found throughout India and Pakistan, Nepal, Myanmar, Thailand and Sri Lanka. It is also found on the Malay Peninsula, Java, and Australia [6]. In India it is found in dry forests throughout Central and Western India, from Bihar as far West as Jammu and Western Peninsula [3].

Plant Description:

H. isora is a small tree or shrub, from 5 to 8 meters tall. It has gray bark and leaves arranged alternately, hairy, ovate, with serrated edges. Its flowers are reddish-brown or orange-red, and its fruits are green when raw, brown, or gray when dry and twisted, with a screw at the sharp end. The seeds of the plant are black or brown and are very polished, roughly rhomboid and rectangular or triangular [7]. Flower pollinators include the jungle stammer, the golden-leafed bird, the gray drongo and the white-bellied drongo [8]. Fruits, seeds, roots and bark of the plant are used. The flowering time of *H. isora* is from the month of April to December, and the fruiting time is from the month of October to June [9]. Different parts of the *H. isora* plant are shown in Fig. 1.

Figure 1: Different parts of *H. isora* Linn. (A: Plant, B: Flower, C: Immature pod, D: Stem bark and E: Mature pod)

Phytoconstituents

The plant roots contain cucurbitacin B and isocucurbitacin B which are reported to possess cytotoxic activity [5]. Harde PA and Shah MB have determined the oleanolic acid from the roots of *Helicteres isora* Linn by HPLC method [6]. The fruits contain neolignans, helisterculins A and B and helisorin and posses weak inhibitory action against reverse transcriptase from avian myeloblastosis virus [7]. Recently, three major compounds of *H. isora* have been identified which were 4'-*O*- β - D-glucopyranosyl rosmarinic acid, 4,4'-O-di- β-D-glucopyranosyl rosmarinic acid, and 2R-O-(4'-O-β-D-glucopyranosyl caffeoyl)-3- (4-hydroxyphenyl) lactic acid [8]. The leaves contain tetratriacontanyl-tetra-tricontanote, flavones-5, 8-dihydroxy-7,4'-dimethoxyflavone, trifolin and hibifolin [9,10]. It is manifest that the plant has great potentials in treating various diseases. Leaves of this plant contain tannins which are reported to possess anthelmintic activity [11]. The preliminary phytochemical screening of the fruit and bark of *Helicteres isora* contained the presence of polyphenols, tannins, carotenoids, flavonoid, carbohydrates, proteins, fibres, and minerals such as calcium, phosphorus and iron [12]. The fruit of *Helicteres isora* contained more amounts of polyphenols, ascorbic acid and carotenoids than the bark. The bark contained more amounts of tannins, flavonoids, α-tocopherol and reduced glutathione when compared to the fruit. Among the nutrients, the fruit contained more amounts of phosphorus and the bark contained significant quantities of total carbohydrates, calcium and iron than the fruit [12,13]. The phytochemical screening of flower *Helicteres isora* revealed that presence alkaloids, carboxylic acid, coumarins, tannins, phenol, xanthoproteins, and carbohydrates [14]. Phytochemical analysis of the methanolic extract of *Helicteres isora* fruits revealed the presence of three major constituents such as sanguinarine, berberine chloride and muscimol [15].

Table 3: Phytoconstituents of *Helicteres isora* Linn.

Sr. No.	Plant part	Phytoconstituents	Reference
1	Roots	Cucurbitacin B, Isocucurbitacin B, and Oleanolic acid	[5, 6]
2	Fruits	Neolignans, Helisterculins A, Helisterculins B, Helisorin, 4'-*O*- β - D-glucopyranosyl rosmarinic acid, 4,4'-O-di- β-D-glucopyranosyl rosmarinic acid, 2R-O-(4'-O-β-D-glucopyranosyl caffeoyl)-3- (4-hydroxyphenyl) lactic acid, Sanguinarine, Berberine chloride and Muscimol	[7, 8, 15]
3	Leaves	Tetratriacontanyl-tetra-tricontanote, Flavones-5, 8-dihydroxy-7,4'-dimethoxyflavone, Trifolin and Hibifolin	[9, 10]
4	Fruit and Bark	Polyphenols, Tannins, Carotenoids, Flavonoid, Carbohydrates, Proteins, Fibres, andnd Minerals such as Calcium, Phosphorus and Iron	[12]
5	Flowers	Alkaloids, Carboxylic acid, Coumarins, Tannins, Phenol, Xanthoproteins, and Carbohydrates	[14]

Table 4: Structures of important chemical constituents in *Helicteres isora* Linn

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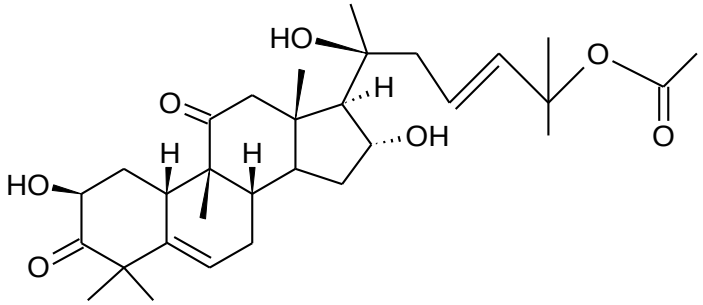
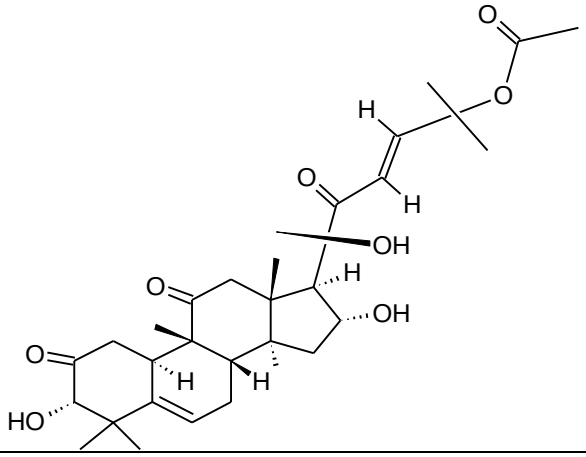
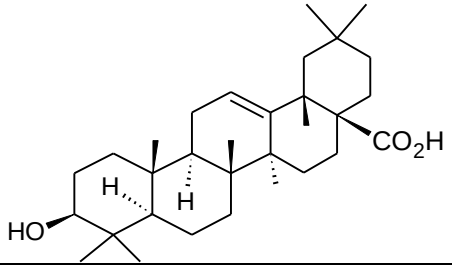
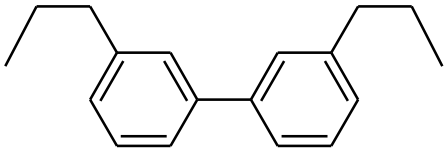
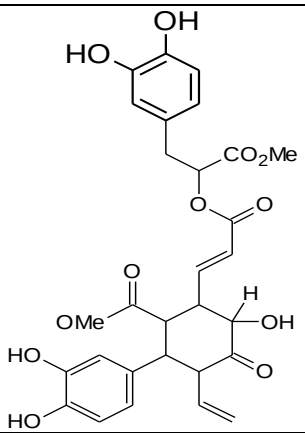
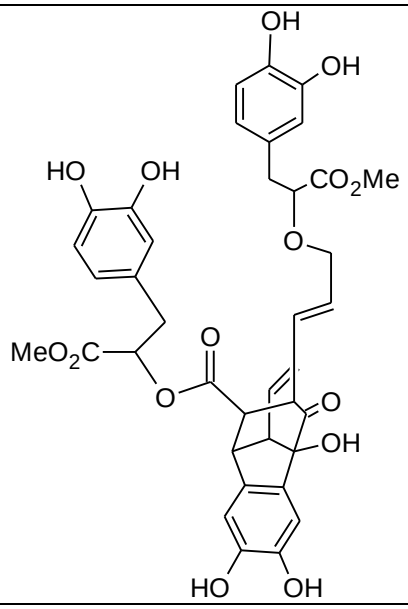
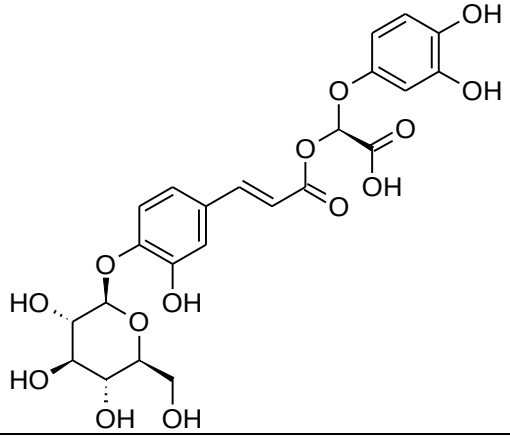
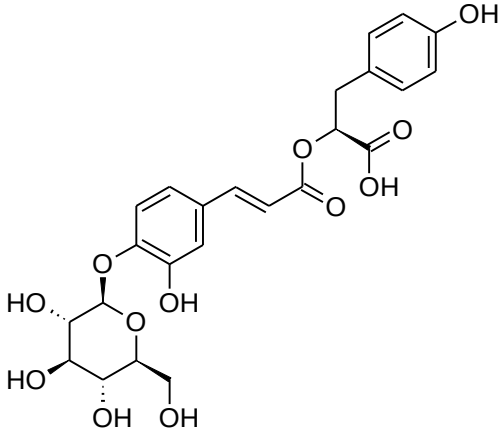
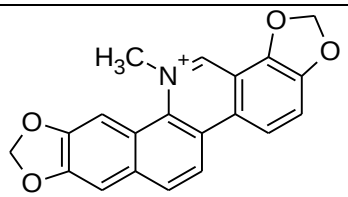
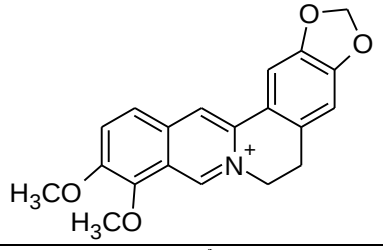
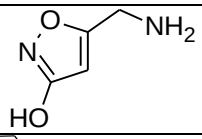
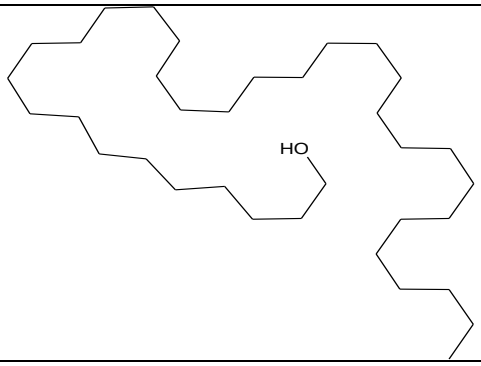
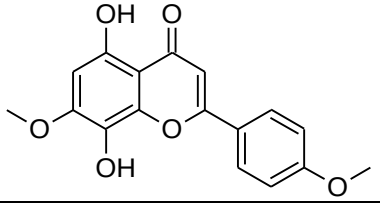
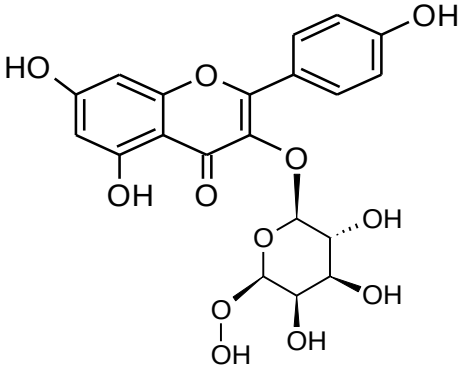
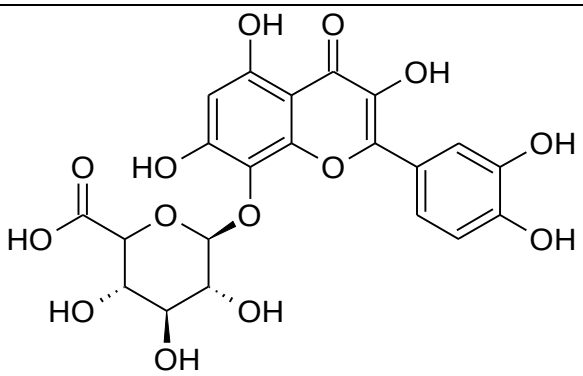
Sr. No.	Chemical Constituent	Structure
1	Cucurbitacin B	

2	Isocucurbitacin B	
3	Oleanolic acid	
4	Neolignans	
5	Helisterculins A	

6	Helisorin	
7	4'-*O*- β - D-glucopyranosyl rosmarinic acid	
8	2R-O-(4'-O-β-D-glucopyranosyl caffeoyl)-3- (4-hydroxyphenyl) lactic acid	
9	Sanguinarine	

10	Berberine	
11	Muscimol	
12	Tetratriacontanyl-tetra-tricontanote	
13	Flavones-5, 8-dihydroxy-7,4'-dimethoxyflavone	
14	Trifolin	
15	Hibifolin	

1. Antidiabetic and Hypolipidaemic Activity

Chakrabharti *et. al.,* revealed the antidiabetic and hypolipidemic activity of ethanolic extract Helicteres isora L. of roots in Swiss albino mice. Ethanollic extract of Helicteres isora L. root produced a significant decrease in plasma glucose, triglycerides and insulin at a dose of 300 mg/kg after 9 days of administration to insulin-resistant and diabetic mice. Ethanolic extract of Helicteres isora L. root has insulin-sensitizing and hypolipidemic activity and also has the potential to treat Type - II diabetes mellitus [16]. Kumar G and Murugesan AG reported that the hypolipidemic activity of aqueous bark extract of Helicteres isora L. in diabetic rats induced by streptozotocin. Administration of Helicteres isora bark extract at doses of 100 and 200 mg/kg for 21 days revealed a significant decrease in serum and tissue cholesterol, phospholipids, fatty acids, and triglycerides in streptozotocin-induced diabetic rats. Also, a significant increase in high-density lipoproteins (HDL) while lowering the level of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). Bark extracts of *Helicteres isora* L. at a dose of 200 mg/kg have a better lipid-lowering effect than 100 mg/kg [17]. Suther *et. al.,* evaluated the antidiabetic activity of *Helicteres isora* Linn Fruits. The antidiabetic effect was studied using in vitro glucose uptake in the isolated rat hemidiaphragm model [18]. Kumar G *et. al.,* reported the hypoglycemic activity of the aqueous extract of the bark of *Helicteres isora* L. in normal, glucose-loaded and streptozotocin-induced diabetic rats. In normal rats, the aqueous extract of the bark of *Helicteres isora* L. in doses of 100 mg/kg/p.o. showed a decrease in blood glucose from 64.5 to 48.5 mg% and 67 to 47 mg% after 2 hours of oral extract and also a significant reduction in blood glucose levels in streptozotocin-induced diabetic rats of 68 to 105 mg% and 66 to 85.5 mg% after 21 days of daily oral administration of the extract. The results expressed that the aqueous extract of the bark of *Helicteres isora* L. contains a potential hypoglycemic action in diabetic rats [19]. Venkatesh *et. al.,* showed the antihyperglycemic and lipid-lowering activities of root extracts of Helicteres isora L. in alloxan-induced diabetic rats. They reported that oral administration of butanol and aqueous extracts of Helicteres isora L. at a dose of 250 mg/kg for 10 days it shows a significant reduction of blood glucose, total cholesterol, triglycerides and urea in alloxan-induced diabetic rats [20].

2. Antibacterial Activity

Gayathri Devi *et. al.,* evaluated antibacterial activity of Methanolic extract of *Helicteres isora* L. fruits and bark. The both fruits and bark extract showed significant antibacterial activity against *Bacillus subtilis, Pseudomonas aeruginosa*, *Proteus vulgaris* and moderate antibacterial activity against *Bacillus subtilis, Pseudomonas aeruginosa*, *Paratyphii A* and *Staphylococcus aureus*. The petroleum ether extract showed considerable activity against *Paratyphii B*, *Salmonella typhimurium* and *E.coli.* Benzene extracts has been found to be effective against *Paratyphii B* and *E. coli,* while the choloroform and acetone extracts has been observed to be ineffective against most of the organisms tested. Hence, methanolic extract showed more significant antibacterial activity as compared to petroleum etheter, benzene, cholorform and acetone extracts [21]. Varghese *et. al.,* performed isolation and evaluation of antimicrobial properties of isolated phytoconstituents of fruits of *Helicteres isora* Linn. Minimum inhibitory concentration (MIC) value of methanolic extract against *Pseudomonas aeruginosa* and *Staphylococcus aureuswas* has found to be 10µg/ml and 8µg/ml respectively [22]. Shriram V. *et. al.,* evaluated antibacterial and antiplasmid activity of *Helicteres isora* L. fruits [23]. Tambekar *et. al.,* revealed antibacterial activities of aqueous, acetone, ethanol and methanol extracts of fruits of *Helicteres isora*. The fruit aqueous extracts of *H. isora* showed prominent antibacterial activities against *E.coli, Staphylococcus epidermidis*, *Salmonella typhimurium* and *Proteus vulgaris*; moderate activity against *Enterobacter aerogenes, Staphylococcus aureus, Salmonella typhi* and least activity against *Pseudomonas aeruginosa.* The aqueous extract showed maximal, the ethanol and methanol extract showed moderate and acetone extracts showed least antibacterial activities [24].

3. Antioxidant Activity

Kumar TM *et. al.,* evaluated the antioxidant activity of acetone, hexane and iso-propyl alcohol extract of *Helicteres isora* Linn fruits. Acetone extract of *Helicteres isora* fruits showed strong antioxidant activity as compared to hexane and iso-propyl alcohol [25]. Manke MB *et. al.,* revealed in-vitro antioxidant activity of methanolic and petroleum ether extracts of *Helicteres isora* Linn. fruits. Antioxidant activity was determined by 2, 2-diphenyl-1-picryl hydrazyl (DPPH) and Hydrogen peroxide (H_2O_2) radicals scavenging assays. The DPPH free radical scavenging activity was obtained with the methanol extract (IC_{50} 42.95 µg/ml), while petroleum ether extract showed less free radical scavenging activity (IC50 89.81µg/ml) as compared to standard ascorbic acid (IC_{50} 23.75 µg/ml). Hydrogen peroxide decomposition activity of methanol and petroleum ether extracts were showed in a concentration dependent manner with an IC_{50} 36.61 µg/ml and 74.40 µg/ml respectively, while IC_{50} value for ascorbic acid was 9.64 µg/ml. Methanol extracts showed potent antioxidant activity than petroleum ether extracts [26]. Kumar V. *et. al.,* reported that the fruits of *Helicteres isora* have broad-spectrum antioxidant potential against free radicals and significantly ameliorated various

impairments associated with free radical formation including lipid peroxidation, protein oxidation and DNA damage. The plant extracts showed concentration-dependent free radical scavenging activities and lipid peroxidation inhibition. Amongst all four extracts, aqueous-methanol extract showed highest antioxidant potential in terms of reducing power (360 ± 5.9 gallic acid equivalent), total antioxidant activity (150 ± 5.6 gallic acid equivalent), scavenging of free radicals including DPPH (75.6%) and OH (100%) in addition maximal (97.4%) lipid peroxidation inhibition at concentration of 1000 µg/ml [27]. Free radicals are known for DNA strand breaking and damage which eventually contributes to carcinogenesis, mutagenesis and cytotoxicity [28]. Kumar G. *et. al.,* evaluated effect of *Helicteres isora* bark extracts on brain antioxidant status and lipid peroxidation in streptozotocin diabetic rats. A significant increase in the activities of plasma insulin, superoxide dismutase, catalase, glutathione peroxidase, glutathione s-transferase, and reduced glutathione were observed in the brain on treatment with 100 mg/kg b.w. and 200 mg/kg b.w. of *Helicteres isora* bark extract and tolbutamide for 5 weeks in streptozotocin diabetic rats. Both *Helicteres isora* bark extracts and standard drug showed a significant decrease in thiobarbituric acid reactive substances and hydroperoxides formation in brain, suggesting that the role of *Helicteres isora* bark extracts in protection against lipid peroxidation-induced membrane damage [29]. Basniwal *et. al.,* investigated in-vitro antioxidant activity of hot aqueous extract of *Helicteres isora* L. fruits. The hot aqueous extract of *Helicteres isora* L. fruits showed significant antioxidant activity by inhibiting nitric oxide and scavenging superoxide anion as well as hydrogen peroxide radicals when compared with different standards like L-ascorbic acid, quercetin and rutin [30]. Polani *et. al.,* evaluated the antioxidant activity of aqueous, ehanolic and methanolic extracts of *Helicteres isora* fruits. The methanolic extract of fruit showed the maximal, aqueous extract showed the moderate and ethanolic extract showed least radical scavenging activity [31]. Vennila *et. al.,* revealed the in-vitro antioxidant activity of Helicteres isora L. The antioxidant activity has found in hexane, chloroform and methanol extracts of Helicteres isora. Among these three extracts, the chloroform extract showed maximal antioxidant activity than the methanol extract and hexane extract [32]. Suthar *et. al.,* evaluated antioxidant activity of hot water extract of *Helicteres isora* showed maximum activity with IC_{50} value 25.12 ± 0.18 µg/ml for 1, 1-diphenyl, 2-picryl hydrazyl assay method, and low activity with IC_{50} value 740.64 ± 4.76 µg/ml for microsomal lipid peroxidation assay. In the β-carotene-linoleate model, the extract showed 45.63% antioxidant activity [18].

4. Antifungal and Anti-biofilm Activity

Jain *et. al.,* evaluated the antifungal activity of stem bark of *Helicteres isora* Linn. The effect of methanol and petroleum extracts of stem bark of *Helicteres isora* Linn had been investigated in five different fungus i.e. *Cryptococcus neoformans, Candida tropicalis, Trychophyton rubrum, Microsporum furfures,* and *Epidermophyton floccosum*. The methanol extracts exhibited significant antifungal activity; while the petroleum ether extracts exhibited weak antifungal activity [33]. Manke MB *et. al.,* evaluated antifungal activity of methanol and petroleum ether extracts of fruits of *Helicteres isora* Linn against planktonic and biofilm growth of *Candida albicans*. Methanol extract of *Helicteres isora* Linn showed complete prevention of planktonic growth at 2 mg/ml, while petroleum ether extract had no effect up to 4 mg/ml concentration. Decrease in biofilm formation was analyzed in presence of 1 mg/ml methanol exteact, and 2 mg/ml concentration of it prevented biofilm formation significantly ($p<0.05$). In comparison, the methanol extract of *Helicteres isora* Linn fruits showed anti-biofilm activity in *C. albicans* while petroleum ether extract exhibited negligible activity against biofilm [34].

5. Anticancer and antitumor activity

Varghese *et. al.,* evaluated the anticancer activity of chloroform extract of *Helicteres isora* L. fruits. The drug has potent action against human breast cancer and anticancer activity of drug is due to presence of alkaloids and flavonoids [35]. Kumar TM *et. al.,* reported the anticancer activity of *Helicteres isora* Linn fruits solvent extracts. Acetone extract of *Helicteres isora* fruits showed better anticancer activity against human lung cancer cells while acetone and crude protein extracts showed anticancer activity against reactive oxygen species [25]. Pradhan *et. al.,* revealed *Helicteres isora* against normal human blood lymphocytes by micronucleus assay and antitumor activity against B16F10 melanoma cell line by Trypan blue exclusion assay for cell viability. Lymphocyte culture treated with 50% methanol extract of *Helicteres isora* showed very less percentage of micronucleus i.e. 0.007% as compared to standard drug doxorubicin which showed 0.018% micronucleus and 50% methanol extract of *Helicteres isora* showed antitumor activity at the concentration 300 µl/ml [36].

6. Anti-inflammatory activity

Badgujar *et. al.,* revealed the potent anti-inflammatory activity of *Helicteres isora* L. stem bark extracts in albino rats. The methanol and petroleum ether extract of stem bark *Helicteres isora* L. has screened for anti-inflammatory activity by using carrageenan induced inflammation in albino rats. The methanol extract (100 mg/kg) showed

56.14% inhibition of rat paw oedema, while petroleum ether extract showed 36.84% inhibition. Methanol extract showed significant anti-inflammatory activity as compared to petroleum ether extract [37]. Rattanamaneerusmee *et. al.,* reported anti-inflammatory activity of *Helicteres isora* L. fruits extract. Anti-inflammatory activity of extracts was studied on the levels of nitric oxide (NO), tumor necrosis factor alpha (TNF-α), production of prostaglandin E2 (PGE- 2), and cyclooxygenas-2 (COX-2). The results revealed that hexane extract showed the strongest activity on PGE-2 production with 69.68 ± 0.017% inhibition followed by 80% ethanol extracts with 57.17 ± 0.021% inhibition compared to celecoxib, the drug acted as COX-2 inhibitor. Dichloromethane extracts possessed high inhibitory activity on COX-2 production at 106.58 ± 0.003% followed by 80% ethanol extracts with 56.58 ± 0.003% inhibition compared to celecoxib. Hexane extract of *H. isora* fruit exhibited activity against TNF-α production with 51.61 ± 0.79% inhibition at 100 µg/mL [38].

7. Antipyretic activity

Tiwari *et. al.,* evaluated antipyretic activity of alcohol and aqueous extracts of *Helicteres isora* L. roots. Antipyretic activity using yeast induced pyrexia model was performed on Wistar rats of either sex. Pyrexia was induced by subcutaneous injection of 20% w/v of brewer's yeast in distilled water. Both alcohol and aqueous extracts at a dose level of 200 and 400 mg/kg b.w. showed significant antipyretic activity within 30 min. of drug administration. [39].

8. Antispasmodic Activity

Pohocha N and Grampurohit ND revealed antispasmodic activity of the fruits of *Helicteres isora* Linn. The antispasmodic activity was determined in-vitro on guinea-pig ileum against three spasmogens acetylcholine, histamine and barium chloride. The activity was compared with standard antispasmodic agents, atropine and diphenhydramine hydrochloride. The activity was also studied in-vivo by observing the gastrointestinal motility in mice using the marker technique. The results indicated that *Helicteres isora* Linn fruits possess potent antispasmodic activity [40].

9. Cardiotonic Activity

Dama *et. al.,* performed the comparative cardiotonic activity of *Helicteres isora* Linn fruits with digoxin on isolated frog heart. The preliminary study was confirmed that *Helicteres isora* showed better cardiotonic activity as compared to digoxin because *Helicteres isora* has rapid onset of action as compared to digoxin. Further study confirmed that *Helicteres isora* has reduced toxicity than the digoxin and this was an advantage *Helicteres isora* over the digitalis [41].

10. Antinociceptive Activity

Venkatesh *et. al.,* evaluated antinociceptive activity of *Helicteres isora.* Helicteres isora roots extract have studied for antinociceptive activity on acetic acid-induced writhing test in mice, at a dose of 250 mg/kg. Petroleum ether, chloroform and aqueous ethanol extracts have showed significant antinociceptive activity. Phytochemical analysis of the active extracts indicated that their major constituents are sterol, triterpenoids (petroleum ether extract) and their glycosides (chloroform and aqueous ethanol extracts), which could be responsible for observed antinociceptive activity [42].

11. Hepatoprotective Activity

Giang *et. al.,* has evaluated **hepatoprotective activity of *Helicteres isora* ethanol extract against paracetamol-induced liver injury in mice.** Ethanol extract of *H. isora* L. (250, 500 and 1000 mg/kg b.w. per day) significantly restored the **paracetamol**-induced alterations in the biochemical activities of blood and liver tissues. The hepatoprotective effect of *H. isora* L. was also confirmed by the histopathological examination of liver tissue. Histopathological examination of liver sections in mice administered with 1000 mg/kg b.w. per day doses of the extract were perfectly protected almost similar to those of untreated mice [43]. Chitra MS and Prema S have evaluated Hepatoprotective activity of *Helicteres isora* Linn against CCl_4 induced hepatic damage in rats. The parameters have studied serum total bilirubin, total protein, alanine transaminase, aspartate transaminase as well as alkaline phosphatase activities. Ethanolic root extract showed significant protection against CCl_4 induced hepatocellular injury [44].

12. Anti-protoscolice Activity

Nabaa *et. al.,* revealed in-vitro anti-protoscolice activity of the boiled water extract of *Helicteres isora* L. fruits. The boiled water extract for the *H.isora* fruits with a concentration of 300 mg/ml revealed most reliable in eliminating the viability of protoscolices after 192 hours at a percentage of 23%, compared with the albendazole drug at a percentage of 0% after 120 hours. *H. isora* fruits boiled water extract could be used as replacement chemotherapy to treat cyst hydatide infection [45].

13. Wound Healing Activity

Renuka M. and Prakash I. reported wound healing potential of *Helicteres isora* Linn leaf extracts. Wound healing activity of petroleum ether, chloroform, acetone, ethanol and hydroalcoholic extracts of *Helicteres isora* Linn leaves were evaluated by incision and excision wound rat models. The hydroalcoholic extract showed significant ($P < 0.05$) wound healing activity [46].

14. Anthelmintic Activity

Manke MB *et. al.,* revealed in-vitro anthelmintic activity of methanolic and petroleum ether extracts

of *Helicteres isora* Linn. fruits. *In-vitro* anthelmintic activity of methanol and petroleum ether extracts of *Helicteres isora* fruits were determined by the evaluation of time for paralysis and death (min.) against Indian earthworms *Pheretima posthuma*. Various concentrations of extracts were tested in the bioassay (10, 20, and 50 mg/ml). Albendazole at concentration 20 mg/ml was included as standard reference while normal saline (0.9 % NaCl) solution as control. Methanol extracts showed potent anthelmintic activity than petroleum ether extracts [26]. Tannins, a polyphenolic compound, have been reported to exhibit anthelmintic activity as they have ability to bind free proteins in the gastro intestinal tract of host animal or glycoprotein on the cuticle of the parasite and cause death of worms [26, 47]. Manke MB *et. al.*, evaluated anthelmintic potential of *Helicteres isora* bark extract in Indian adult earthworms. Earthworms were grouped and treated with extract at concentration of 10, 20 and 50 mg/mL, albendazole of 10 mg/mL as standard and normal saline as a control. The paralysis time and death time was considered as indicator of anthelmintic activity. All the extracts showed concentration dependent activity but significant activity was observed at 50 mg/mL. The extract showed better activity at concentration of 50 mg/mL with paralysis time (12.54 min) and death time (16.55 min) when compared to standard albendazole. The study revealed that the methanolic extract of *H. isora* bark have potent anthelmintic activity against Indian adult earthworms [48].

15. Anti-diarrheal activity

The fruit has demulcent, astringent, and antispasmodic effect that are useful in the gripping of bowels and flatulence of infants and children. The bark, root and seeds are used for dysentery and diarrhea [49].

16. Treatment of Snakebites

Aqueous and ethanol extracts of *Helicteres isora* has evaluated for *in vitro* enzyme-inhibition activity against enzymes. *Naja naja* venom neutralization assay has evaluated by minimum indirect hemolytic dose (MIHD) assay and *in vitro* tissue damaging method. Ethanolic extract of *Helicteres isora* exhibits *Naja naja* venom enzyme-inhibition activity [50].

Table 6: Reported pharmacological actions of *Helicteres isora* Linn.

Sr. No.	Part used	Reported activity	Solvent used for extraction	Reference
1	Roots	Antidiabetic and hypolipidemic activity	Ethanol	[16]
2	Bark	Hypolipidemic activity	Aqueous	[17]
3	Fruits	Antidiabetic and antioxidant activity	Hot water	[18]
4	Bark	Hypoglycemic activity	Aqueous	[19]
5	Roots	Antihyperglycemic and lipid-lowering activity	Butanol and aqueous	[20]
6	Bark and Fruits	Antibacterial activity	Petroleum ether, benzene, cholorform and acetone	[21]
7	Fruits	Antimicrobial activity	Methanol	[22]
8	Fruits	Antibacterial and antiplasmid activity	Acetone	[23]
9	Fruits	Antibacterial activity	Aqueous, acetone, ethanol and methanol	[24]
10	Fruits	Antioxidant and anticancer activity	Acetone, hexane and iso-propyl alcohol	[25]
11	Fruits	Anthelmintic and antioxidant activity	Methanol and petroleum ether	[26]
12	Fruits	Antioxidant activity	Aqueous, aqueous methanol, methanol and acetone	[27]
13	Bark	Brain antioxidant and lipid peroxidation	Aqueous	[29]
14	Fruits	Antioxidant activity	Hot aqueous	[30]
15	Fruits	Antioxidant activity	Aqueous, ehanol and methanol	[31]
16		Antioxidant activity	Hexane, chloroform and methanol	[32]
17	Bark	Antifungal activity	Methanol and petroleum ether	[33]
18	Fruits	Antibiofilm activity	Methanol and petroleum ether	[34]
19	Fruits	Anticancer activity	Chloroform	[35]

20	Fruits	Antitumor activity	Methanol	[36]
21	Bark	Anti-inflammatory activity	Methanol and petroleum ether	[37]
22	Fruits	Anti-inflammatory activity	Hexane, dichloromethane	[38]
23	Roots	Antipyretic activity	Alcohol and aqueous	[39]
24	Fruits	Antispasmodic activity	Dichloromethane	[40]
25	Fruits	Cardiotonic activity	Distilled water	[41]
26	Roots	Antinociceptive activity	Petroleum ether, chloroform and aqueous ethanol	[42]
27	Arial parts	**Hepatoprotective activity**	Ethanol	[43]
28	Roots	Hepatoprotective activity	Ethanol	[44]
29	Fruits	Anti-protoscolice activity	Boiled water	[45]
30	Leaves	Wound healing activity	Petroleum ether, chloroform, acetone, ethanol and hydroalcoholic	[46]
31	Bark	Anthelmintic activity	Methanol	[48]
32	Bark, root and seeds	Anti-diarrheal activity	-----	[49]
33	Fruits	Snake bite	Ethanol	[50]

Conclusion

The pharmacotherapeutic efficiency of Helicteres isora Linn widely used in the indigenous system of medicine. It has been established through modern testing and evaluation such as pre-clinical and clinical studies in different diseased conditions. The plant contained the presence various important preliminary phytochemicals such as polyphenols, tannins, carotenoids, flavonoid, alkaloids, steroids, saponins, coumarins, carbohydrates, proteins, fibres and minerals and also various important chemical constituents such as Cucurbitacin B, Isocucurbitacin B, Oleanolic acid, Neolignans, Helisterculins A, Helisterculins B, Helisorin, 4'-O- β - D-glucopyranosyl rosmarinic acid, 4,4'-O-di- β-D-glucopyranosyl rosmarinic acid, 2R-O-(4'-O-β-D-glucopyranosyl caffeoyl)-3- (4-hydroxyphenyl) lactic acid, Sanguinarine, Berberine, Muscimol, Tetratriacontanyl-tetra-tricontanote, Flavones-5, 8-dihydroxy-7,4'-dimethoxyflavone, Trifolin and Hibifolin which has used as the key substances for management of multiple disorders. Further studies are needed to establish the mechanism of action of these chemical constituents and more detailed cohort studies at both laboratory and clinical levels are necessary for the development of *H. isora* containing herbal formulations or in combination with other herbs to fight multiple diseases.

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ASSESSMENT OF QUALITY OF LIFE IN PATIENTS UNDERGONE ANGIOPLASTY AND TAKING TICAGRELOR: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND INFORMATION

Acute Coronary Syndrome encompasses life-threatening conditions including STEMI, NSTE, NSTEMI, and UA. Ticagrelor, an antiplatelet drug, reduces cardiac events but increases bleeding risk. DAPT with ticagrelor and aspirin is recommended post-PCI, with the duration determined by individual factors. Comprehensive prospective studies are essential to assess ticagrelor's real-world effectiveness and impact on patients' quality of life**.**

MATERIALS AND METHODS

A six-month cohort study was conducted at the Sri Jayadeva Institute of Cardiovascular Sciences and Research with 288 participants based on specific criteria. Subject enrolment was based on the inclusion of patients above 18 years of age undergoing angioplasty and the exclusion of lactating, pregnant women along with other severe comorbid conditions (HIV, COPD). Data were collected, including patient demographics, medical history, and medication records. Quality of life was assessed using the SF36 scale, documented in Microsoft Excel.

RESULTS

The study was conducted at a 350-bed tertiary care teaching hospital, Out of 750 ACS patients, 350 had angioplasty, and 288 were selected based on specific criteria. Gender distribution showed 76.04% male, suggesting a higher male prevalence. ACS categorization revealed 24.30% with Inferior Wall Myocardial Infarction, 1.38% with Posterior Wall Myocardial Infarction, and 24.65% with Anterior Wall Myocardial Infarction. SF-36 questionnaire indicated improvements in some aspects but deterioration in others over two months.

CONCLUSION

There was a significant benefit of using ticagrelor in patients undergoing angioplasty as it showed less prevalent side effects. In a few aspects, the quality of life showed an improvement. Furthermore, patient counseling is required for a better outcome.

Keywords: Ticagrelor; Acute Coronary Syndrome; Angioplasty: Safety.

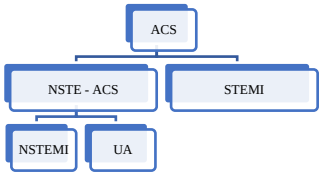
1. INTRODUCTION

The European Society of Cardiology (ESC) and the American Heart Association (AHA) provide guidelines for the management of Acute Coronary Syndrome (ACS), which recommend the inclusion of antiplatelet therapy alongside percutaneous coronary intervention. In modern medical practice, ticagrelor is a commonly used antiplatelet medication for the treatment of ACS. Being a P2Y12 inhibitor, ticagrelor blocks platelet activation and aggregation, reducing the risk of arterial thrombosis. Besides lowering the risk of adverse cardiovascular events, it is known for its faster onset and offset of action. Though ticagrelor has remarkable benefits, it also has certain risks that may include dyspnea and bleeding. Therefore, ticagrelor must be employed considering the individual characteristics of patients like age, bleeding risk, comorbidities, and potential drug interactions.

Acute coronary syndrome (ACS)

Acute coronary syndrome is a subcategory of coronary artery syndrome that presents symptoms such as Prinzmetal angina and frequent myocardial infarction. It is a life-threatening emergency condition that is mainly caused because of reduced blood flow to the heart. It is a common type of cardiac disease that affects approximately one million people throughout the world. Based on

electrocardiographic (ECG) changes, ACS can be categorized as follows:



Angioplasty

A diagnostic technique called an angiogram employs X-ray imaging to identify the kind and location of a blockage in the heart or blood vessels.

"Angioplasty" means to employ a balloon to widen a clogged or constricting artery. In current practice, a stent is placed during the surgery and remains there permanently to improve blood flow. Percutaneous transluminal coronary angioplasty (PTCA) is another name for coronary angioplasty. Percutaneous coronary intervention is the term used when coronary angioplasty and stenting are performed together. A catheter with a small balloon attached to its tip is introduced into a blood vessel and guided to the blocked coronary artery as part of the surgery. The balloon is inflated at the point of occlusion once the catheter has been positioned. As a result, there is greater room for blood flow since the thrombus or plaque is compressed against the artery walls. Before inserting the balloon, a little expandable metal mesh coil (stent), if stenting is necessary for the stenosis, will be put around it. The stent will then be deployed at the location of the intervention. This prevents arterial blockage from happening again. A layer of vascular tissue begins to develop on top of the stent after it has been implanted. Depending on the kind of stent, it can take three to twelve months for the artery tissue to align perfectly with the stent. Antiplatelet medications may be administered to stop restenosis. Infection at the catheter insertion site, bleeding at the catheter insertion site (typically the wrist, arm, or groin), hypersensitivity reaction to the contrast dye, blood clot within the treated blood vessel, damage to the treated blood vessel caused by the catheter, rupture of the coronary artery, complete closure of the coronary artery, need for open-heart surgery, occasionally abnormal heart rhythms, stroke, chest pain, or other complications are some of the risks associated with stenting or angioplasty.

DAPT

Dual antiplatelet therapy (DAPT) involves two types of antiplatelet agents, where one drug is aspirin and the other is a P2Y12 receptor inhibitor.

Ticagrelor Monotherapy

Recent studies show ticagrelor monotherapy was associated with a lower risk for major bleeding compared with standard DAPT, without a concomitant increase in ischemic events.

Quality of Life in patients taking Ticagrelor, undergone angioplasty

The impact of ticagrelor on the quality of life in patients undergoing angioplasty can vary based on several variables, including each patient's health status, reaction to therapy, and lifestyle.

Positive Effects on Quality of Life:

Reduced risk of major cardiovascular events: By minimizing blood clots and decreasing the risk of heart attacks and strokes, ticagrelor could potentially be likely to enhance the patient's sense of psychological well-being and optimism regarding their cardiovascular health.

Better disease management: By taking ticagrelor as prescribed, patients may feel a greater sense of control over their condition, leading to improved psychological well-being.

Negative Effects on Quality of Life:

Medication Adherence: The need to take ticagrelor regularly and the potential side effects may affect medication adherence, which could impact treatment efficacy and patient outcomes.

METHODOLOGY

Study site:

The study was conducted at Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru

Study design:

The study was a cohort study.

Study period The study was carried out for a period of six months from April 2023 to September 2023.

Ethical approval:

Ethical clearance was obtained from the institutional ethics committee of Sri Jayadeva Institute of Cardiovascular Sciences and Research.

Sources of data:

- Medical and Medication records of the patient
- Interviewing patient and caretaker
- Telephonic contact or direct meeting with the patient if needed
- Various questionnaires
- Any other relevant source

Study criteria:

Inclusion criteria:

- Patients aged 18 years and above
- Patients undergoing angioplasty
- Patients who are on ticagrelor medication

Exclusion criteria:

- Pregnant or lactating women.
- Severe comorbid conditions (end-stage renal disease, advanced cancer, HIV infection, severe COPD).
- Incomplete case sheets and medication information.
- Patients who are not willing to participate in the study.

Study procedure:

Preparation of data collection form:

A data collection form was suitably designed that includes all relevant data of the enrolled patients, such as patient name, IP number, unit name, gender, age, phone number, date of admission, and date of discharge. Objective evidence collected were vitals like blood pressure (BP), pulse, body temperature, respiratory rate, oxygen saturation (SPO2), and ejection fraction (EF); laboratory data such as haematology, electrolytes, biochemistry, lipid profile, and cardiac biomarkers along with 2D echocardiography and Doppler test, coronary angiogram (CAG) and percutaneous transluminal coronary angioplasty (PTCA). Certain questionnaires such as SF36 scale was used.

Informed consent:

An informed consent form was designed in English and the same was translated into the regional language that is Kannada to acquire consent from patients who will be enrolled in the study. The study was properly explained to the patients. In illiterate patients the study aspects were explained to the caretakers and consent was obtained willingly.

Patient enrolment:

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.

Data collection:

The in-charge authority of cardiology 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.

SF36 questionnaire:

SF36 is a questionnaire used to assess the quality of life of patients. We interviewed patients in the hospital using the SF36 form after they underwent angioplasty and recorded the scores ranging between 0-100. Later we re-interviewed patients over the telephone using the same SF36 form after 2 months from the date of procedure. The scores were compared with the initial assessment of the quality of life of patients and difference was obtained.

Statistical analysis

The data was collected, entered, and segregated in Microsoft Excel. The entered data was analyzed with the help of Excel using descriptive analysis.

RESULTS

The proposed work was carried out in a 350-bed tertiary care teaching hospital for 6 months.

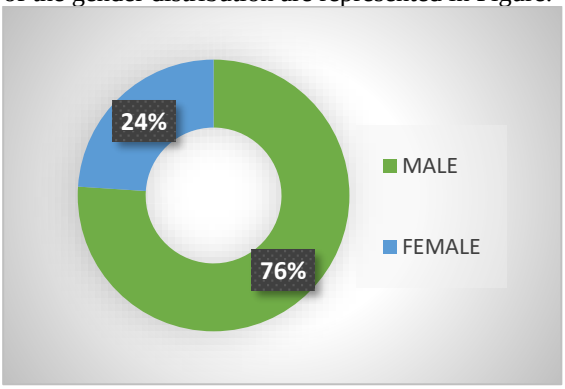
Prevalence of Acute Coronary Syndrome Patients Undergone Angioplasty

There was a total of 750 patients diagnosed with ACS in a month, among which 350 had undergone angioplasty. We selected 288 patients who had undergone angioplasty as our study population (n=288) based on our study criteria.

DIAGNOSIS	FREQUENCY(n)	PERCENTAGE
ACS	750	100%
Angioplasty	350	46.66%

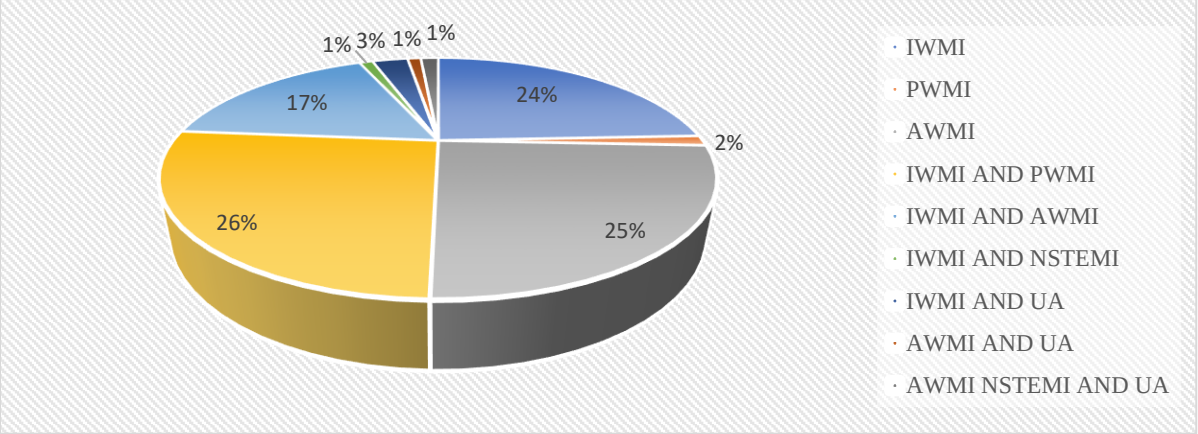
Gender Distribution in the Study

Among the study population (n=288), 76.04% (219) were male and 23.95% (69) were female. The details of the gender distribution are represented in Figure.



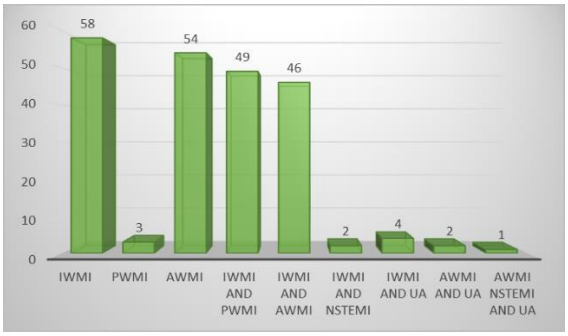
ACS Categorization in the Study Population

Among the study population(n=288), 24.30%(n=70) patients had IWMI, 1.38%(n=4) patients had PWMI and 24.65% (n=71) patients had AWMI. The remaining patients had a combination of two or more diseases such as 26.71% (n=75) patients had IWMI and PWMI, 17.36% (n=50) patients had IWMI and AWMI, 1.48%(n=3) patients had IWMI and NSTEMI, 2.08% (n=6) patients had IWMI and UA, 1.48% (n=3) patients had AWMI and UA and only 2 patients had a combination of AWMI NSTEMI and UA. The details of the ACS categorization are represented in Figure.



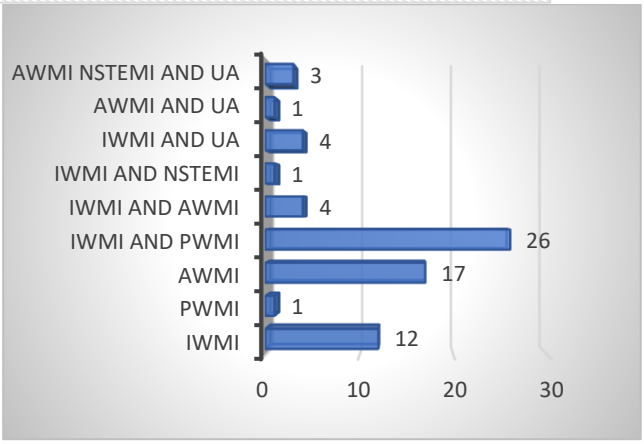
ACS Categorization of Male Patients in the Study Population

Among 219 male patients, 26.48% (n=58) patients had IWMI, 1.36% (n=3) patients had PWMI, 24.65% (n=54) patients had AWMI, remaining patients had combination of two or more diseases such as 22.37% (n=49) patients had IWMI and PWMI, 21.32% (n=42) patients had IWMI and AWMI, 0.91% (n=2) patients had IWMI and NSTEMI, 1.89%(n=4) patients had IWMI and UA, 0.91% (n=2) had AWMI and UA and 0.45% (n=1) patient had a combination of AWMI NSTEMI and UA. The details of the ACS categorization of male patients in the study population are given in Figure



ACS Categorization of Female Patients in the Study Population

Among 69 female patients, 17.39% (n=12) patients had IWMI, 1.44% (n=1) patients had PWMI, 24.63% (n=17) patients had AWMI, remaining patients had combination of two or more diseases such as 37.68% (n=26) patients had IWMI and PWMI, 5.79%(n=4) patients had IWMI and AWMI, 1.44% (n=1) patients had IWMI and NSTEMI, 5.79%(n=4) patients had IWMI and UA, 1.44% (n=1) had AWMI and UA and 4.34% (n=3) patient had a combination of AWMI NSTEMI and UA. The details of the ACS categorization of female patients in the study population are given in Figure



Habits

Alcoholic:

Among the study population (n=288), 30.9% (n=89) were identified as alcoholics and 60.09% (n=199) patients were non-alcoholics. Details of alcoholic and non-alcoholic patients are as follows.

ALCOHOLIC	NO. OF PATIENTS(n)	PERCENTAGE
YES	89	30.9%
NO	199	69.09%

Smoker:

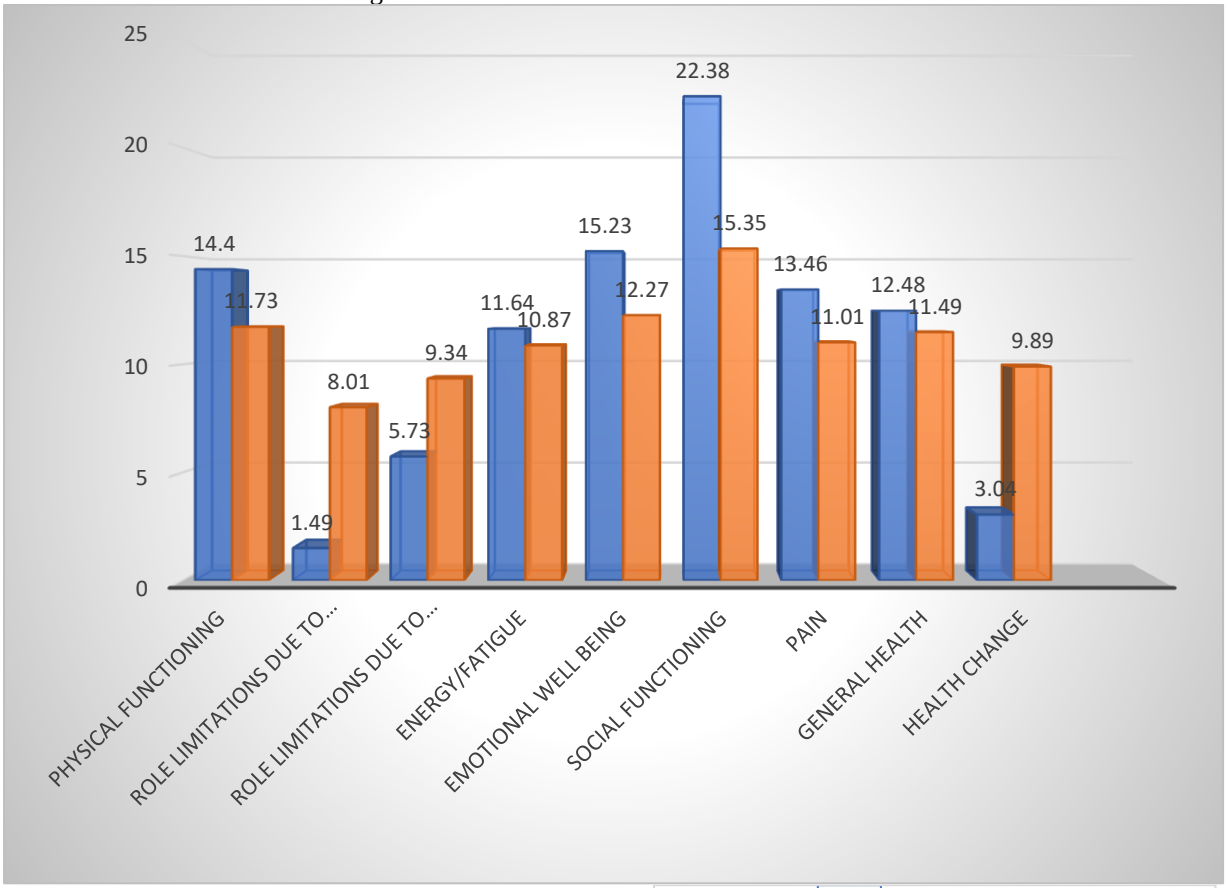
Among the study population (n=288) 43.4% (n=125) were identified as smokers and 56.59% (163) patients were non-smokers. Details of patients who smoke and who do not smoke are given in Table

SMOKING	NO. OF PATIENTS(n)	PERCENTAGE
YES	125	43.4%
NO	163	56.59%

Quality of Life

The quality of life of patients were assessed twice using the SF-36 questionnaire, initially after the patients underwent angioplasty and finally after two

months from the date of angioplasty. The quality of life was calculated based on 9 domains and scores were given from the range 0 to 100. The mean of the initial quality of life was as follows: physical functioning was 14.4, role limitations due to physical health were 1.49, role limitations due to emotional problems was 5.73, energy/fatigue was 11.64, emotional well-being was 15.23, social functioning was 22.38, the pain was 13.46, general health was 12.48 and health change was 3.04. The mean of the final quality of life was as follows: physical functioning was 11.73, role limitations due to physical health were 8.01, role limitations due to emotional problems was 9.34, energy/fatigue was 10.87, emotional well-being was 12.27, social functioning was 15.35, pain was 11.01, general health was 11.49 and health change was 9.89. The details of the assessment of quality of life are shown in Figure.

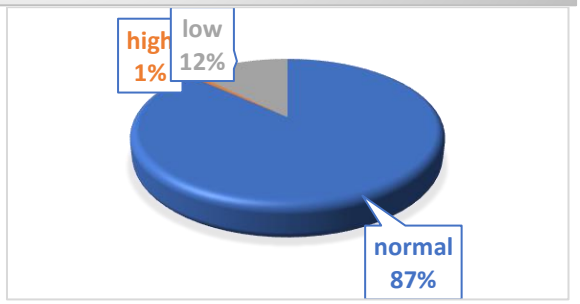


Change in Quality of Life

Difference between the initial and final quality of life was obtained to assess the change in the quality of life of study patients. The difference of 9 domains was as follows; physical functioning – 9.55, role limitations due to physical health – 13.18, role limitations due to emotional problems – 12.21, energy/fatigue – 10.26, emotional well-being – 12.21, energy/fatigue – 10.26, emotional well-being – 9.92, social functioning – 9.78, pain – 9.05, general health – 10.71, health change – 15.3.

Appetite

Among the study population (n= 288) 86.8% (250) patients had a normal appetite, 0.69% (2) patients had high appetite, and 12.5% (36) patients had a low appetite. From the details obtained from the figure, and table, we can say that the drug had no significant effect on appetite.



DISCUSSION

A total of 288 patients who met the study criteria and their case profile sheets were analyzed. The present study set out to assess the quality of life in patients undergoing angioplasty. The study was carried out for 6 months at SJICR, Mysore.

Out of the study population, ACS was found more in men than in women. In a study conducted by Chandrasekhar Dilip, Shinu Cholamugath et.al, similar to our study they found 74% were males and 26% were females in their study population, indicating there was a preponderance of male

patients with ACS. This may be due to the reason that males are more prone to alcohol and smoking, also males are subjected to physical stress than females. The mean average age of patients in the study population was found to be 56.82 ± 10.2 years. An identical result was obtained in the study conducted by Chandrasekhar Dilip, Shinu Cholamugath et.al, where the mean age of the population was found to be 62.57 years ± 12.18 years.

CONCLUSION

Ticagrelor is primarily used for the treatment of Acute Coronary Syndrome (ACS). Among the cases collected, the common sub-classifications of ACS that is being treated with ticagrelor are ST segment Elevation Myocardial Infarction (STEMI) and Non ST segment Elevation Myocardial infarction (NSTEMI).

Although studies have proven that ticagrelor is not associated with any mortality, it has a risk of bleeding and is being used rampantly in patients diagnosed with ACS, especially those who have undergone angioplasty.

From the above discussed study, it was found that certain aspects of quality of life, such as role limitations due to physical health, role limitations due to emotional problems, and health change, improved over a two-month period following angioplasty. However, other domains deteriorated, which included physical functioning, energy/fatigue, emotional well-being, social functioning, pain, and general health.

The study also comprises of the data on prevalence of ACS patients undergoing angioplasty which shows that among 750 patients diagnosed with ACS, 350 patients underwent angioplasty that is 46.66% of the total ACS population.

This study provides valuable insights into the prevalence, and quality of life among ACS patients who underwent angioplasty in a tertiary care teaching hospital. These findings contribute to our understanding of ACS management and can inform healthcare providers in tailoring treatment approaches for this patient population. However, it's important to note that further research and larger-scale studies are needed to confirm and expand upon these findings.

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A CROSS-SECTIONAL STUDY ON THE PREVALENCE OF ADVERSE DRUG REACTIONS OF SODIUM VALPROATE USED AS A MOOD STABILIZER IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER IN A TERTIARY CARE HOSPITAL.

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ABSTRACT:

Objectives: To determine the prevalence of ADRs and to analyse the causality, severity and preventability of ADRs associated with sodium valproate in BPAD patients.

Methods: A cross-sectional study was carried out in KR Hospital, Mysuru for a period of 6 months. After taking the consent the patients were interviewed to gather ADRs of sodium valproate, which were then recorded using the UKU SERS scale. ADRs associated were evaluated for causality, severity, and preventability using Naranjo's Algorithm, Modified Hartwig and Siegel scale, and Modified Shumock and Thornton scale respectively and recorded.

Results: Our study included 142 study population. Male preponderance (65.49%) was observed. A total of 368 ADRs were identified using UKU-side effect rating scale among the study population. The most common ADRs observed were increased

sleep (11.41%), weight gain (8.69%), sexual dysfunction (8.69%), headache (7.33%). 69.57% of reactions were possible, 75.27% of ADRs were assessed as mild and 94.29% of ADRs were definitely preventable. Prevalence of ADRs was found to be 85.91%.

Conclusion: ADRs are a frequent occurrence in patients with BPAD who are taking sodium valproate which is mild in most cases. Early detection and management can reduce the frequency of ADRs, increase compliance, and enhance patient quality of life.

INTRODUCTION:

Sodium valproate is a well-established anticonvulsant medication that has been repurposed for the management of mood disorders, particularly bipolar disorder. Like any medication, it can cause ADRs in some individuals. So through this study, we are making an attempt to access knowledge about ADRs.

World Health Organization (WHO) defines an ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. ADRs have been traditionally divided into two categories: Type A reactions, also known as Augmented reactions, are 'dose-dependent' and Type B reactions, often known as Bizarre reactions.

Bipolar disorder is a serious mental health condition characterized by recurrent episodes of depression, hypomania, and/or mania, which are typically interspersed with periods of relatively normal mood and functioning.

According to a global study on mental health, bipolar disorders were prevalent across all cultures and racial/ethnic groups, with lifetime prevalence rates of 0–6% for bipolar I disorder, 0–4% for bipolar II disorder, 1–4% for subthreshold bipolar disorder, and 2–4% for the full spectrum of bipolar disorders.

There are three types of bipolar disorder. Bipolar I disorder, Bipolar II disorder Cyclothymic disease. Manic Episode: A manic episode is a period of at least one week during which a person has more energy than normal, is extremely elated or agitated most of the time. Symptoms include reduced need for sleep, larger or more rapid speech, when speaking, have erratic or uncontrollably rushing thoughts or change topics quickly, Distractibility, Increased activity, such as restlessness or juggling multiple tasks at once a rise in dangerous behaviour (such as reckless driving and shopping binges). Hypomanic Episode: Less intense manic symptoms that just need to persist for four days.Episode of Major Depression: Extreme melancholy or despair, Loss of interest in once-enjoyed hobbies; feelings of shame or unworthiness, Fatigue, Either more or less sleep, Decreased appetite, Pacing or agitation, or slowed speech or movement, difficulty in paying attention, recurring suicidal or death thoughts.

Sodium valproate: Among the various drugs used for mood stabilization, sodium valproate has emerged as a prominent and effective treatment option. It is a well-established anticonvulsant medication that has been repurposed for the management of mood disorders, particularly Bipolar disorder.

MATERIALS AND METHOD:

Study site: Krishna Rajendra Hospital, a tertiary care hospital attached to Mysore Medical College & Research Institute, Mysuru.

Study design: The study was designed to be a cross sectional observational study. The sample size of the study was 142 patients.

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

Ethical approval: Institutional Human Ethical Committee of Mysore Medical College and Research Institute, Mysuru approved the study.

Study criteria:

Inclusion criteria:

1. Patients of age group 18 years – 75 years.
2. Patients of either gender.
3. Patients diagnosed with bipolar disorder according to International Classification of Diseases (ICD-11) criteria.
4. Patients taking sodium valproate for Bipolar Affective Disorder.

Exclusion criteria:

1. Those patients not willing to give informed consent.
2. Pregnant women
3. Lactating women

Source of data: All the relevant and necessary data will be collected from Interviewing patients and caretakers, Prescription of the patient, Communicating with concerned clinicians and health care professionals, Medical and Medication records of the patient

Study procedure: The study involved the following steps: -

1. Preparation of informed consent form (ICF): An appropriate ICF was created in both English (Annexure 1) and Kannada (Annexure 2) to gain patients' informed consent to participate in the study for those who are fulfilling the study criteria. A committee charged with upholding institutional Ethics evaluated and approved the ICF. The patient was fully informed about the study in their regional languages, and their consent was obtained by taking their signature or thumb impression.

2. Preparation of data collection form (DCF): For the study, a specially created data collection form (Annexure 3) was developed. The form included demographic details like name, age, gender, family history of psychiatric illness, education, occupation, income, diet, social habits, residence, and contact information. Clinical information such as the diagnosis, co-morbidities, adverse drug reactions and therapeutic information such as the name of the prescribed drug, dose, frequency, route, and duration of administration, as well as the use of concurrent drugs also were considered. To document the ADRs due to Sodium Valproate Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Annexure 4) was used. assessment the Causality, Severity and Preventability of recorded ADRs were done using Naranjo's algorithm (Annexure 5), Modified Hartwig and Seigel scale (Annexure 6), Modified Shumock and Thornton scale(Annexure 7) respectively.

3. Patient enrollment: Patients who met the criteria for the study were included once their Informed Consent was obtained and translated into their regional or preferred language. Enrolment took place during OPD visits of patients.

4. Data collection: First and foremost, patients were interviewed in their regional languages. All relevant details of the enrolled patients were obtained from the aforementioned data sources and documented in the Data collection form (Annexure 3). The patients were interviewed once when they are attending OPD to gather ADRs of sodium valproate, which were then recorded using the UKU scale (Annexure 4). ADRs associated with sodium valproate were evaluated for causality, severity, and preventability using Naranjo's Algorithm, Modified Hartwig and seigel scale, and Modified Shumock and Thornton scale respectively and recorded.

5**. Statistical analysis:** A descriptive statistics was presented in terms of frequency and percentages for

categorical value. Mean, was used to describe the general characteristics of the study sample. An inferential statistic was be done by using chi-square test. In chi-square test p value ≤0.005 is considered as significant.

RESULTS:

A total of 142 study participants from the Psychiatry OPD who met our inclusion criteria were analysed.

Demographic Data:

The study population comprised of 65.49%(n=93) of males and 34.50% (n=49) females. Maximum patients belongs to the age group of 26-35 years(n=41).

PREVALENCE OF ADRs:

The prevalence of ADRs was found to be 85.91%. The prevalence of psychiatric and metabolic ADRs was found to be same (51.40%).Least prevalent ADRs were Blood related (1.40%), and vision related(3.52%).

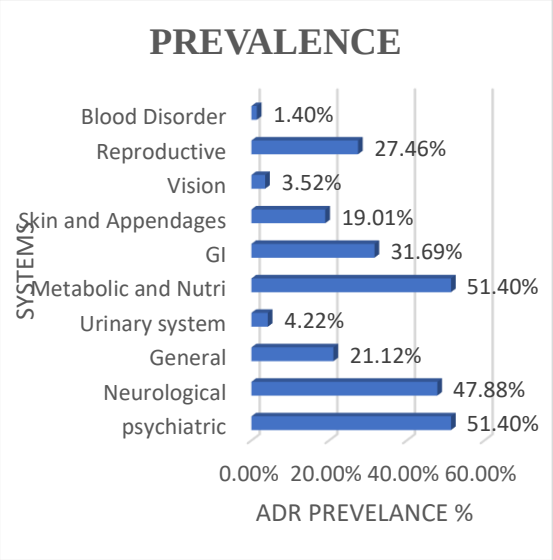

Figure 1: ADR Prevalence percentage distribution

Distribution of ADRs:

Out of 142 patients, 122(85.91%) patients developed one or more ADRs. The percentage of patients developing ADRs was slightly more in males (86.02%; n=80) as compared to females (85.71%; n=42). The most common ADR observed was Increased Sleep comprising 11.41%(n=42) of total ADRs. The other frequently seen ADRs included weight gain(n=32;8.69%), sexual dysfunction(n=32;8.69%), Xerostomia(n=27;7.33%), Headache(n=27;7.33%), Tremors(n=23;6.25%), Photosensitivity(n=23;6.25%), Anorexia(n=21;5.70%), weightloss(n=20;5.43%), Myalgia(n=17;4.61%) as depicted in figure 1.

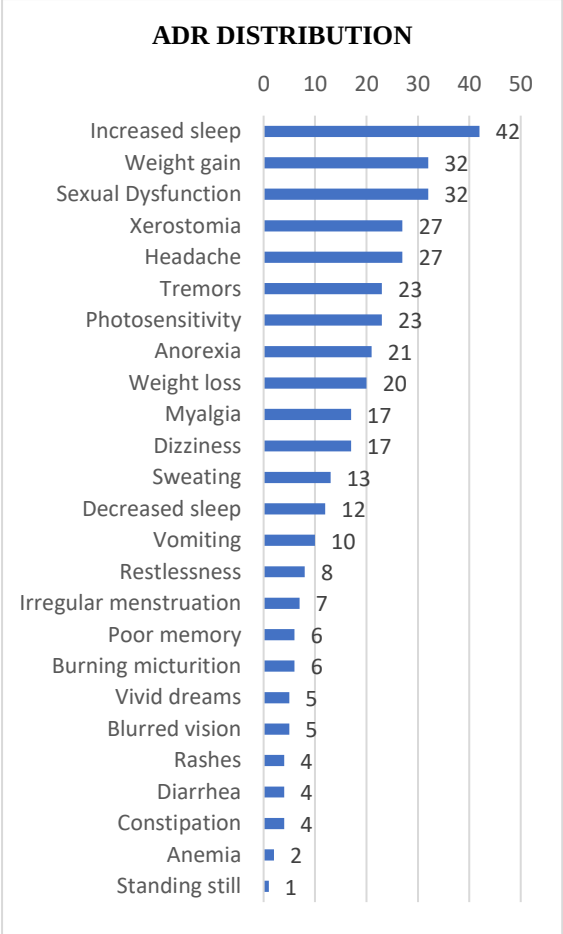

Figure 2: ADR Distribution among the study population.

According to the UKU side effect rating scale ADRs belonging to the group of other side effects (n=115; 33.23%)like Erectile dysfunction, Ejaculatory dysfunction, Menstrual irregularities, Weight gain, and Photosensitivity etc.were most common followed by Autonomic side effects(n=87;25.14%) like orthostatic dizziness, micturition disturbances, accomodation disturbances, xerostomia etc. 75 were psychic side effects(21.67%) like decreased and increased sleep, vivid dreams, failing memory etc. and 69 were neurological side effects(19.94%) like tremors, dystonia, headache etc. as shown in figure 3.

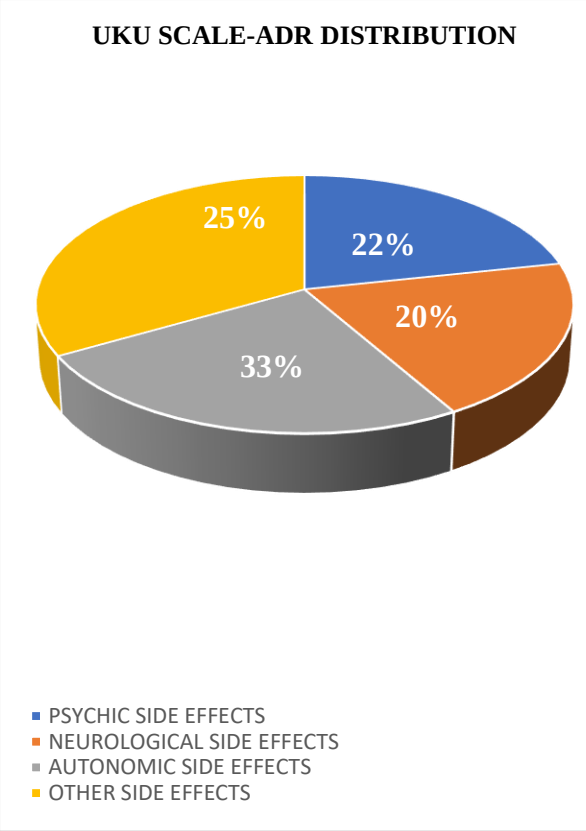

Figure 3: Distribution of ADRs according to UKU-Scale(n=346). (*Anemia and Anorexia were not included in this evaluation as they are not a part of the standard UKU Side effect rating scale.)

According to the UKU Side effect rating scale, most of the ADRs belong to Degree 1(n=250;72.25%) followed by Degree 2(n=95;27.45%) and Degree 3(n=1; 0.28%) based on the degrees specified in the UKU scale which is depicted in the figure 4.

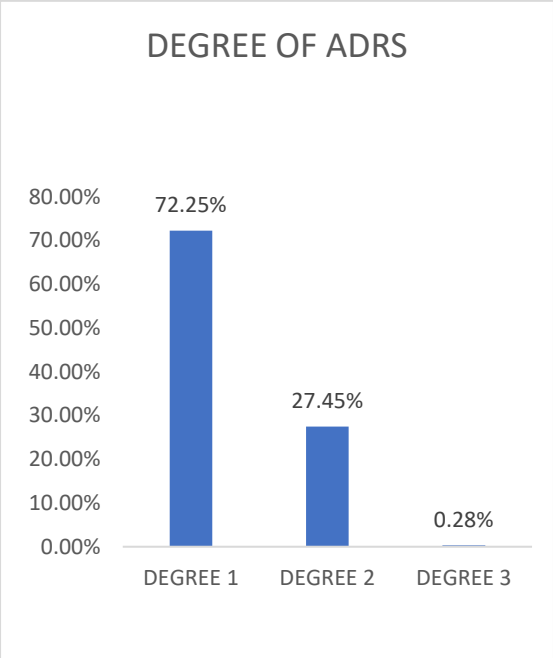

Figure 4:Degree of ADRs according to UKU Scale(n=346).
(*Anemia and Anorexia were not included in this evaluation as they are not a part of the standard UKU Side effect rating scale.)

The below table gives the various organ system affected by ADRs to WHO- adverse reaction terminology.

Sl. No	SOC(WHO-ART SOC Code)	Percentage of ADRs (n=368)	Adverse Drug reactions (No.of patients affected)
1.	Psychiatric disorders (0500)	19.83% (n=73)	Filing memory(6), Decreased sleep(42), increased sleep(12), vivid dreams(5), Restlessness(8),
2.	Neurological Disorders (0400)	18.47% (n=68)	Myalgia(17), Headache(27), Tremor(23), Standing still(1)
3.	Body as a whole- general disorders (1810)	8.15% (n=30)	Sweating(13), Dizziness(17)
4.	Urinary system disorders (1300)	1.63% (n=6)	Micturition disturbances(6)
5.	Metabolic and Nutritional disorders (0800)	19.83% (n=73)	Weight gain(32), Weight loss(20), Anorexia(21)
6.	Gastrointestinal disorders (0600)	12.22% (n=45)	Vomiting(10), Diarrhea(4), Constipation(4), Xerostomia(27)
7.	Skin and appendages disorders (0100)	7.33% (n=27)	Photosensitivity(23), Rashes(4)

8.	Vision disorders (0431)	1.35% (n=5)	Blurred vision(5)
9.	Reproductive disorders (1400)	10.59% (n=39)	Sexual dysfunction(32), Menstrual irregularities(7)
10.	Blood disorders (1200)	0.54% (n=2)	Anemia(2)

Table I: ADR distribution according to organ system.

CAUSALITY ASSESSMENT:

Causality Assessment of ADRs was done using Naranjo's Algorithm (Annexure 5). Out of 368 ADRs identified from the study population, majority of the ADRs were found to be Possible (n=256; 69.57%). Around 26.90% (n=99) of ADRs were found to be Probable and n=13; 3.53% of ADRs were identified as Unlikely. No ADRs belonged to Definite.

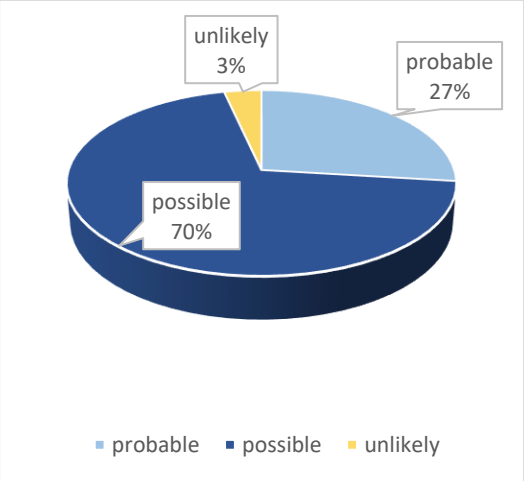

Figure 5: Causality distribution according to Naranjo's Algorithm.

SEVERITY ASSESSMENT:

Severity assessment of ADRs were done using Modified Hartwig and Siegel Scale (Annexure 6). Out of 368 ADRs 277 were found to be mild (n=277;75.27%). Among mild ADRs Level 1 ADRs were found to be 201 (54.62%) followed by Level 2 (n=76;20.65%). In Moderate ADRs Level 3 ADRs were found to be 91(24.72%). No ADRs belonged to Level 4(a), Level 4(b) and Severe.

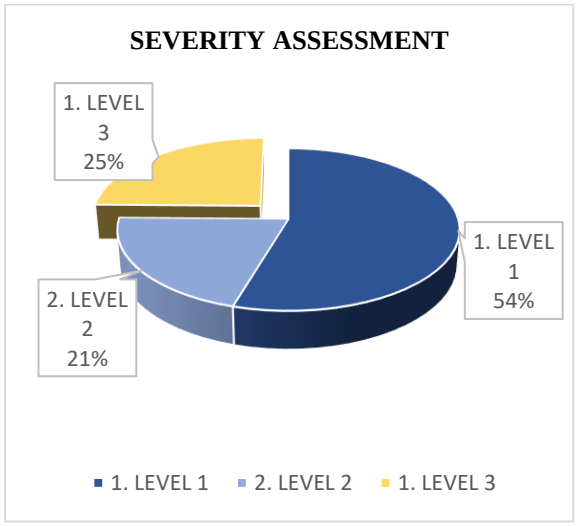

Figure 6: Severity distribution according to Modified Hartwig and Siegel Scale.

PREVENTABILITY ASSESSMENT

Preventability of ADRs among the study participants was assessed by using Modified Shumock and Thornton Scale (Annexure 7). Out of 368 ADRs 347 (94.29%) were Definitely preventable and 21 (5.70%) were probably preventable.

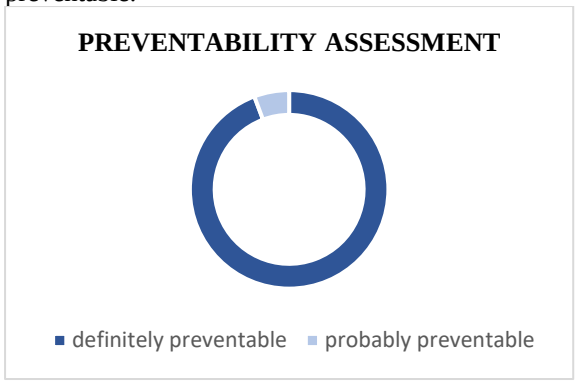

Figure 7: Preventability Distribution according to Modified Shumock and Thornton Scale

RISK FACTOR ASSOCIATION WITH ADRs:

Factors		ADRs		Chi-square value	p-value
		Yes	No		
Age	≤35 years (n=67)	60	7	1.3862	0.2389

	>35 years(n=75)	62	13		
Gender	Male(n=93)	80	13	0.0025	0.9600
	Female(n=49)	42	7		
Education	Illiterate (n=27)	25	2	1.2283	0.2677
	Literate(n=115)	97	18		
Employment Status	Employed (n=59)	51	8	0.02300	0.8794
	Unemployed (n=83)	71	12		
Diet	Veg(n=41)	35	6	0.0143	0.9045
	Non veg(n=101)	87	14		
Family Hx of psychiatric illness	Family Hx(n=35)	35	0	7.6145	0.0057*
	NoFamily Hx(n=107)	87	20		
Other medical illness	Present(n=31)	27	4	0.0457	0.8306
	absent(n=111)	95	16		
Marital Status	Single(n=45)	36	9	1.9050	0.1675
	Married (n=97)	86	11		
Substance Abuse (Alcohol)	Alcoholics (n=38)	34	4	0.5428	0.4612
	Non alcoholics (n=104)	88	16		
Substance Abuse (smoking)	Smokers(n=25)	23	2	0.9282	0.3353
	Non smokers (n=117)	99	18		
Substance Abuse (Others)	Users(n=2)	2	0	0.3325	0.5641
	Non users(n=140)	120	20		
Disease State	BPAD I(n=104)	91	13	0.8063	0.3692
	BPAD II(n=38)	31	7		
Treatment	Monotherapy(n=22)	19	3	0.0043	0.9475
	Polytherapy(n=120)	103	17		

Table II: Risk factor association with ADRs

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A PROSPECTIVE STUDY ON COMBINATION OF OLANZAPINE OR RISPERIDONE WITH FLUOXETINE AND THEIR IMPACT ON QUALITY OF LIFE IN PSYCHOSIS PATIENTS.

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ABSTRACT:

Objectives: To assess the quality of life, medication adherence and the ADRs in psychosis patients taking a combination of olanzapine with fluoxetine and risperidone with fluoxetine.

Methods: A six-month prospective observational cohort study with 100 participants on antipsychotics was conducted at Krishna Rajendra Hospital, Mysuru, in 2023. Data, including quality of life, ADRs, and medication adherence, was collected and assessed using SF-12, Naranjo scale, and MARS-10.

Results: The study encompassed 100 participants, with those aged 36-45 (29%) more prone to psychosis. Males (52%) exhibited higher susceptibility than females (48%), and higher literacy levels (65%) increased the risk. Weight range 51-70kg (74%) was common, and most with psychosis were non-alcoholic (93%) and non-smokers (85%). Regimens improved quality of life and medication adherence. Adverse drug reactions included sleeplessness (13.02%) and weight gain (13.02%), with a total of 307 reported, 201 deemed probable and 106 possible.

Conclusion: The study population shows strong adherence, indicating the efficacy and tolerance of the current medication regimen. Findings underscore the need to address both physical and mental health for overall wellbeing. Emphasizing ADR assessment aids physicians in safe treatment selection, necessitating an active surveillance system for identifying and reporting ADRs linked to antipsychotic medicines

INTRODUCTION:

Due to the country's rapid demographic and epidemiological transformation, the burden of neurological illnesses is also anticipated to rise in India. 14.3% of the population in India, or 197.3 million people, suffer from a mental disorder. [1]Psychiatric disorders are a broad category of mental health conditions that affect a person's thoughts, feelings, actions, and daily functioning. Schizophrenia and bipolar disorder have been labels for the functional psychoses, the most severe psychiatric diseases with adult onset, for more than a century. [2] Psychosis is a prominent symptom associated with numerous psychiatric, neurodevelopmental, neurologic, and medical conditions, which makes it a crucial area for diagnosis and treatment in neurologic and psychiatric practises. PSYCHOSIS Symptoms include: Hallucinations and Delusions Disorganised thoughts, Disorganised behaviour, Catatonia and Negative symptoms

Schizophrenia is a severe behavioural disorder that affects 24 million people around the world, or 1 in 300 folks. Schizophrenia can have a significant impact on all aspects of life, including personal, family, social, academic, and economic life. It also causes psychosis and can lead to severe impairment. [5]

A major mood condition called bipolar disorder is characterised by recurrent episodes of depression that alternate with periods of hypomania and/or mania, usually separated by intervals of mood and functioning that are more or less normal. Bipolar disorder type 1 (BP-I) and type 2 (BP-II) are distinguished in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV: American Psychiatric Association, 1994) by the severity of the manic episode.[10]Depression is characterised by a wide variety of symptoms, including sadness or low mood, absence of interest in activities, lack of strength and energy, feeling weak or weaker, lack of

self-assurance, guilt, helplessness, or hopelessness, difficulty paying attention, restlessness, difficulties sleeping, constant feelings of worthlessness, suicidal thoughts, changes in appetite, irritability, discomfort, tiredness, or weakness despite physical cause and changes in appetite. [13]

Atypical antipsychotic medications have been used more and more frequently in older patients in recent years. These medications have unique receptor binding patterns, good efficacy against negative symptoms, and few side effects, especially in terms of decreased extrapyramidal symptoms. [20]Atypical antipsychotic medications have been used more and more frequently in older patients in recent years. These medications have unique receptor binding patterns, good efficacy against negative symptoms, and few side effects, especially in terms of decreased extrapyramidal symptoms. [20]The primary evidence-based therapy for schizophrenia and other major psychotic illnesses is antipsychotic medication. Antipsychotic drugs usually provide dramatic symptomatic relief for delusions and visions, as well as improvement for disruptive thinking and behaviour.

Psychosis characterized by psychotic symptoms that may arise in conditions like major depressive disorder, bipolar disorder, and schizophrenia. As psychosis is such a complex medical conditions, patients frequently need to have their quality of life evaluated and adhere to treatment plans. Evaluating the patient's quality of life helps to determine the patient's general state of health, comprising their psychological, social, and physical functioning. Knowing this aspect makes it easier to adjust treatment plans to address specific problems and improve patients' overall health and output. Antipsychotics and antidepressants together can help improve psychotic treatment approaches and provide further relief from the depressive symptoms commonly associated with psychosis Treatment adherence is important.

MATERIALS AND METHOD:

Study site: Krishna Rajendra Hospital, a tertiary care hospital attached to Mysore Medical College & Research Institute, Mysuru.

Study design: The study was designed to be a prospective observational study. The sample size of the study was 100 patients.

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

Ethical approval: Institutional Human Ethical Committee of Mysore Medical College and Research Institute, Mysuru approved the study.

Study criteria:

Inclusion criteria:

1. Patients aged 18 to 65 years old.
2. Patients of either gender.
3. Patients receiving Olanzapine with fluoxetine and Risperidone with fluoxetine.
4. Patients diagnosed with psychosis according to ICD 11 criteria

Exclusion criteria:

1. Patients who are not willing to participate.
2. Patients with severe medical conditions that may interfere with the study.
3. Pregnant and lactating women

Source of data: All the relevant and necessary data will be collected from Interviewing patients and caretakers, Prescription of the patient, Communicating with concerned clinicians and health care professionals, Medical and Medication records of the patient

Study procedure: The study involved the following steps: -

1. Preparation of informed consent form (ICF): An inform consent form was designed in English and the same was translated to native speaking language: Kannada for obtaining consent from patients who are willing to participate in the study. The aims and objectives of the study was properly explained to the patient and the consent was obtained. In the case of illiterate patients, the study aspects were explained to care takers and consent acquired from study population.

2. Preparation of data collection form (DCF): A data collection form was properly designed that included all the relevant data including demographic details like name, age, gender, weight, address, phone number ,clinical data such as diagnosis, past medical and medication history, past history of medication adherence and interventions made, co-morbidities, therapeutic data such as name of the drug, dose, frequency, route and duration of administration, concurrent medication(s) from various available data sources and documented in a suitably designed data collection form.

3. Patient enrollment: Patients who met the study criteria were enrolled in the study after obtaining informed consent. Enrolment took place during outpatient visits. Patients who are receiving olanzapine, risperidone, and fluoxetine as part of their treatment were recruited into the study.

4. Data collection: The patient was initially provided the informed consent form, and all the details of the study were described. Each relevant details about the enrolled patients, including demographics (age, gender, family history, etc) and treatment information was gathered from interviews (hospital visit and telephone calls), their medical records and questionnaires and documented in the data collection form.

5**. Statistical analysis:** Microsoft Office Excel 2016 was used for the statistical analysis and evaluation of the data. The descriptive statistics like percentage, mean , tables, graphs are applied

to simulate the outcome of the study and standard deviation is used in the study.

RESULTS:

A total of 100 study participants from the Psychiatry OPD who met our inclusion criteria were examined.

Demographic Data:

The study population comprised between the ages of 36-45y (n=29, 29%) were more likely to experience psychosis. Moreover, it reveals that males (n=52, 52%) exhibit a higher susceptibility to psychosis than females (n=48, 48%) and individuals with higher levels of literacy (n=65, 65%) are at an increased risk of developing the condition. Additionally, the study finds that those with psychosis tend to fall within the weight range of 51-70kg (n=74, 74%) and significant proportion of individuals with psychosis are non-alcoholic (n=93, 93%) and non-smokers (n=85, 85%).

QUALITY OF LIFE:

The quality of life in psychosis patients by using SF-12 scale for 77 subjects who were prescribed with fluoxetine and olanzapine regimen

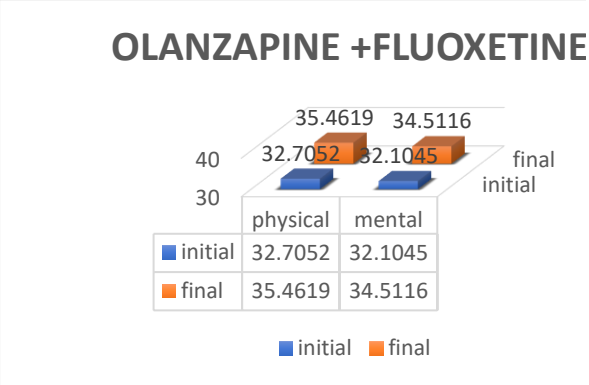

Figure 1: Graphical representation of quality of life within psychosis patients with olanzapine and fluoxetine.

Quality of life in psychosis patients by using SF-12 scale for 23 subjects who were prescribed with fluoxetine and risperidone regimen

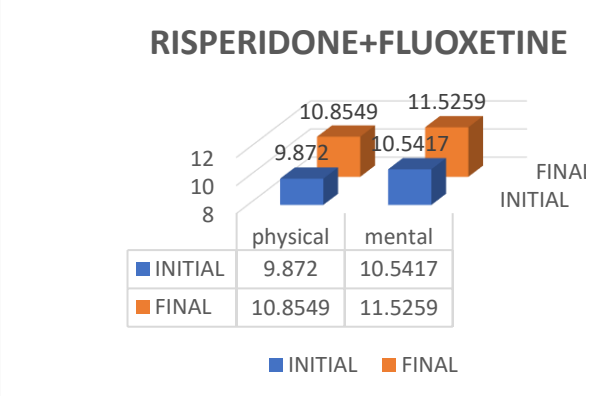

Fig 2: Graphical representation of quality of life within psychosis patients with risperidone and fluoxetine regimen

Quality of life of study population based on age group below 45(18-45) years.

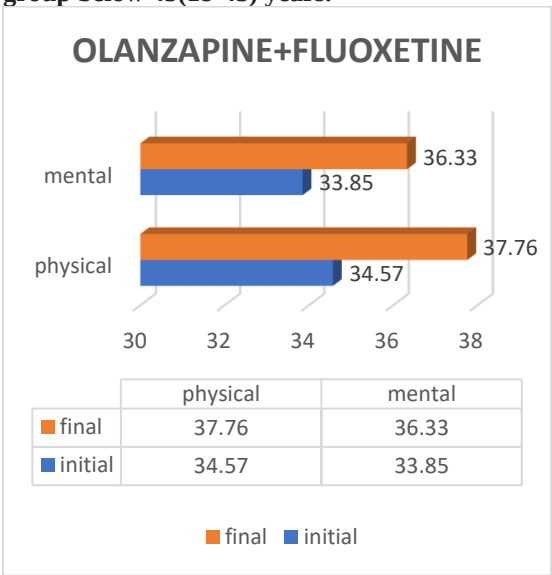

Fig 3: Graphical representation of quality of life of patients within age group 18-45years who were on olanzapine with fluoxetine regimen

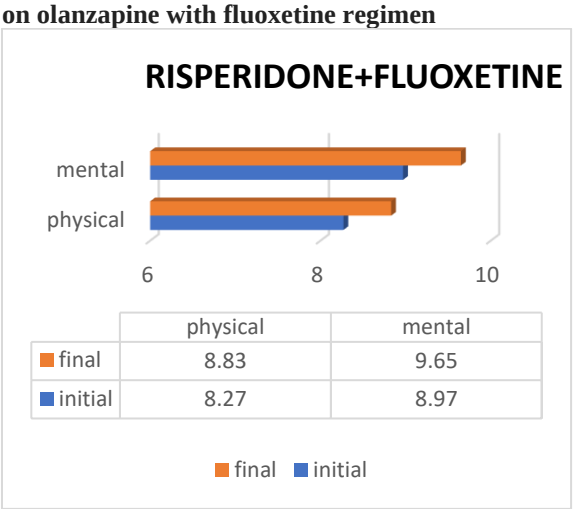

Fig 4: Graphical representation of quality of life of patients within age group 18-45years who were on risperidone with fluoxetine regimen

Quality of life of study population based on age group above 45(46-65) years.

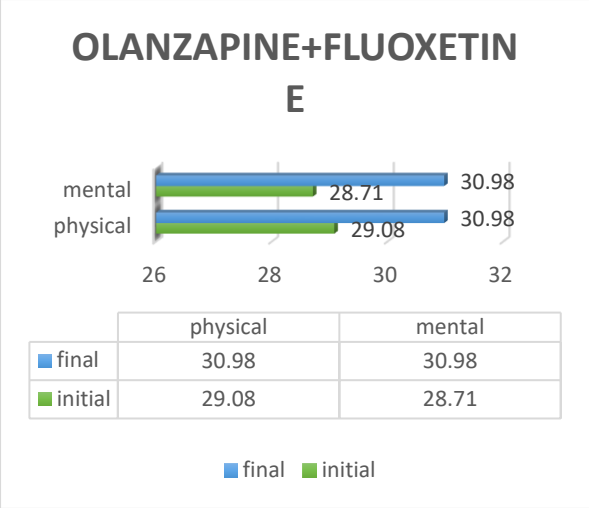

Fig 5: Graphical representation of quality of life of patients within age group 46-65years who were on olanzapine with fluoxetine regimen.

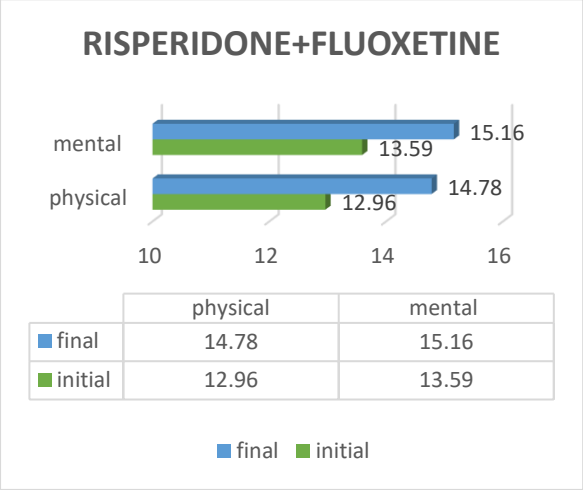

Fig 6: Graphical representation of quality of life of patients within age group 46-65years who were on risperidone with fluoxetine regimen.

MEDICATION ADHERENCE:

The results of the study, which looked at 100 participants using the treatment regimens olanzapine + fluoxetine and risperidone + fluoxetine among individuals with psychosis, showed improved adherence.

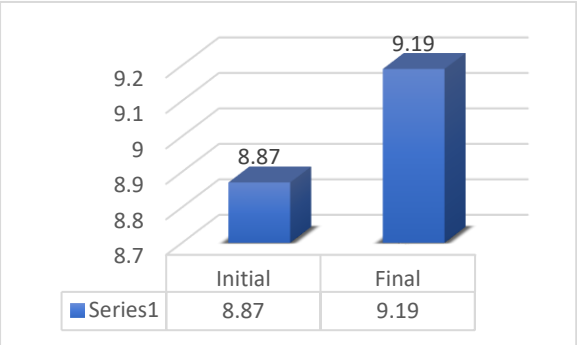

Fig7: Graphical representation of medication adherence within psychosis patients

ADVERSE DRUG REACTION:

Fig 8 illustrates the ADRs quantified by using Naranjo causality assessment scale in the study population. Most patients reported sleeplessness (n=40, 13%) and weight gain (n=40, 13%) followed by fatigue (n=28, 9.12%), headache (n=23, 7.49%) and dry mouth (n=22, 7.16%). The least reported ADRs were diarrhoea, vomiting, tachycardia, asthenia, urinary incontinence and sore throat which was only seen in a patient each.

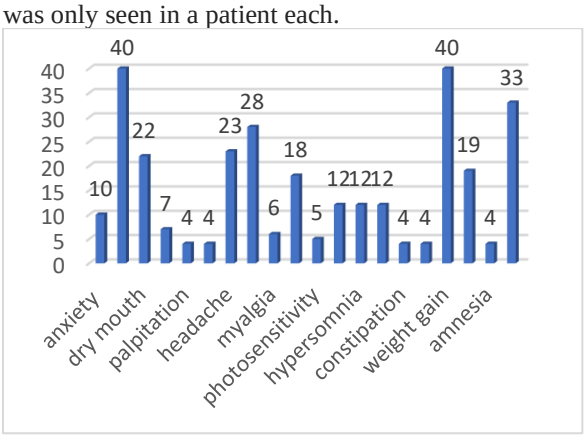

Fig 8: Graphical representation of total number of ADRs in psychosis patients

NUMBER OF PROBABLE AND POSSIBLE ADRS IN THE STUDY POPULATION:

NAME	RESULT
DEFINITE	0
PROBABLE	201
POSSIBLE	106
UNLIKELY	0

Table 1: Details of Naranjo Causality Assessment Scale of Study Population

ORGAN SYSTEM CLASSIFICATION IN STUDY POPULATION OF PSYCHOSIS

According to the MedDRA Organ System Classification, the ADRs were categorized into several classes. Of this, the highest number of ADRs belong to Nervous system (n=70, 22.80%) followed by GI system (n=59, 19.21%) and Metabolic system (n=59, 19.21%) and the least number of ADRs belong to Respiratory system (n=1, 0.32%).

Table 2: Distribution of ADR's based on organ system classification in study population of psychosis

ADRS	NO OF ADRS	PERCENTAGE
CVS	9	2.93%
NERVOUS SYSTEM	70	22.80%
MUSCULOSKELETAL SYSTEM	10	3.25%
GI SYSTEM	59	19.21%
RENAL SYSTEM	3	0.97%
DERMATOLOGICAL SYSTEM	14	4.56%
RESPIRATORY SYSTEM	1	0.32%
REPRODUCTIVE SYSTEM	2	0.65%
METABOLIC SYSTEM	59	19.21%
CIRCULATORY SYSTEM	2	0.65%
OPHTHALMIC SYSTEM	12	3.90%
CNS	66	21.49%

CONCLUSION:

The study population demonstrates a higher level of adherence, which suggests that the current medication regimen is effective and well tolerated by patients. Our findings highlight the importance of addressing both the physical and mental health to enhance the overall wellbeing. It is vital to be familiar with the assessment of ADRs caused by various antipsychotics. It assists physicians in selecting safe treatment and lowering the risk of occurrence of ADRs. As we get more information about ADRs, we require an active surveillance system for identifying and reporting ADRs associated with antipsychotic medicines

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SMICROSPHERE'S: A PROMISING DRUG CARRIER

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Abstract: The targeted drug delivery is designed for endeavoring to concentrate the drug in the tissues of curiosity while reducing relative concentration of medication in the remaining tissues. There for drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. Controlled drug delivery system can overcome the problems of conventional drug therapy and gives better therapeutic efficacy of a drug. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. The range of Techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. Microspheres has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. In future various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Microspheres, Controlled release, Therapeutic efficacy, Novel drug delivery

Introduction:

Microspheres are spherical particles that range in diameter from 10 µm to 1000 µm. Microspheres are essential for improving the way conventional drugs are absorbed and lessening their side effects. The controlled release of the medicinal content is the primary benefit of using microspheres as a drug delivery mechanism. By postponing the medication's release from dose forms, microencapsulation reduces adverse effects and enhances patient adherence. This method uses emulsion solvent diffusion evaporation to coat an aqueous insoluble coat (polymer) over an aqueous insoluble core (drugs) to create a sustained release drug delivery system. There are several methods for creating microspheres, such as phase separation, spray-dry, and emulsification using single or double solvent evaporation systems.

One method for creating microspheres is to dissolve the precursor components in volatile solvents and then disperse them in a different solvent that isn't miscible with the first one. A fine powder known as microspheres that is soluble in water will be produced when the last solvent has completely evaporated. Medication with a brief half-life that is merely transferred from the gastrointestinal tract (GIT) is instantly eliminated from the bloodstream[1]. In order to circumvent this issue, oral sustained or controlled release (CR) has also been created. This method will gradually release the drug into the gastrointestinal tract and maintain a constant level of medicine intensity in the plasma for an extended amount of time. A dose formulation that achieves the necessary plasma therapeutic drug concentration and stays stable over the course of the treatment is considered appropriate. This can be accomplished by administering a conventional dosage form at a predetermined frequency and dose. They have the advantage of not being microcarriers since nanoparticles act locally by migrating into the interstitium within the lymphatic system's 100 nm range.

Most likely, hazardous materials can be carried. Encapsulated, the dried microparticles may be referred to as solids instead of liquids. The intake dose is administered as a series of discrete, small multiarticulate particles, each of which retains and releases a portion of the dosage; hence, the failure of one subunit has no effect on the overall dosage failure. In order to facilitate the release of medication into the skin, microparticles are employed in skin applications. This helps to ensure that the drug stays localized at the application site and does not unnecessarily reach the systemic circulation. They serve as a reservoir that releases an active ingredient gradually over time to keep medication items at an appropriate concentration in the skin while minimizing unwanted side effects. As a result, there are fewer cycles of over- and under-medication. In the treatment of infectious diseases, it is particularly pertinent to the decrease of antibiotic resistance. Additionally, by integrating the product into the proper vehicle, these distribution methods can improve product safety[2].

Materials used:

Polymers are typically utilized as microspheres. They fall into two categories.

1. Synthetic polymers
2. Natural polymers

Synthetic polymers are divided into two types.

1] Non-biodegradable polymers:

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate

- Epoxy polymers

2] Biodegradable polymers:

- Lactides, Glycosides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides[3,4]

Natural polymers obtained from different sources like Proteins, carbohydrates and chemically modified Carbohydrates.

A] Proteins:

- Albumin
- Gelatin
- Collagen

B] Carbohydrates:

- Agarose
- Carrageenan
- Chitosan
- Starch

C] Chemically modified carbohydrates:

- Poly dextran
- Poly starch [5,6]

Advantages of Microspheres:

1] Reduction in size leads to an increase in surface area and can boost the strength of the poorly soluble substance.
2] Reducing dose and risk.
3] Maintaining a constant level of medication in the body to enhance patent compliance.
4] Polymer-based drug packaging keeps the medication from undergoing enzymatic cleavage while allowing it to be used with a drug delivery system.
5] Shorter dosage intervals increase patient compliance[7].

Disadvantages of Microspheres:

1] The modified formulation-based releases.
2] The controlled dosage process's release rate, which varies depending on a number of variables including nutrition and levels of transfer via the intestines.
3] Differences in the rate of discharge between doses.
4] Chewing or breaking these dosage forms is not permitted.
5] There is less reproducibility[8].

Pre-requisites for ideal micro particulate carriers:

The material utilized for the preparation of micro particulate should ideally fulfill the following prerequisites.

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Target ability
- Polyvalent[9]

Types of Microspheres:

Microspheres are classified into different types. They are of following

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

I. Biodegradable polymeric microspheres
II. Synthetic polymeric microspheres

1] Bioadhesive microspheres:

Adhesion is the process by which a medication sticks to a membrane by the use of a water-soluble polymer that has the ability to stick. Bio adhesion is the phrase used to describe the adherence of a medication delivery device to a mucosal membrane, such as the nasal, rectal, ophthalmic, or buccal. These microspheres produce superior therapeutic activity because they stay longer at the application site, form close contact with the absorption site, and have a longer residence time. To have a way to give the drug delivery system and the absorbent membranes close contact, it would be beneficial to manufacture bioadhesive microspheres. Because of its superior bioadhesive qualities, polycarbophil (Noveon® AA1) was choosen as the polymer for the creation of bioadhesive microspheres.[10].

2] Magnetic microspheres:

This type of drug delivery system, which targets the exact location of the sickness, is crucial. A smaller quantity of a medicine with magnetic targeting can take the place of the greater amount of the drug that is freely circulating. Incorporated materials used to create magnetic microspheres respond magnetically to a magnetic field through magnetic carriers. medicines that dissolve in water (lipophilic medicines also require the dispersing agents) and 10 nm magnetite (Fe3O4) particles are combined in an aqueous solvent of the matrix material to create magnetic microspheres. After that, the oil is used to emulsify this combination. To create particles in the appropriate size range, ultrasonication or shearing are used. The matrix is then heated or chemically cross-linked to stabilize it.

I] Therapeutic magnetic microspheres
II] Diagnostic microspheres[11].

3] Floating microspheres:

Because the bulk density of floating kinds is lower than that of gastric fluid, they float in the stomach without slowing down the pace at which the stomach empties. The medication is released gradually at the desired pace if the stomach material is floating in the system, lengthening the duration of gastric residency and causing more variations in plasma concentration. By producing a sustained therapeutic impact, this

approach lowers the frequency of dose. Sink particles will disperse over a wide region of absorption sites with each consecutive gastric emptying, improving the likelihood of a more or less predictable drug release profile and absorption. Furthermore, there is less chance of dosage dumping because each dose is made up of several subunits[12].

4] Radioactive microspheres:

The 10–30 nm-sized microspheres used in radioembolization treatment are bigger than capillaries and are tapped into the first capillary bed they come across. They are injected into the arteries that supply the target tumor. Therefore, in all of these circumstances, radioactive microspheres give specific regions a strong radiation dose without endangering the healthy tissues nearby. There are three different types of radioactive microspheres: those that emit α, β, and γ. The subset of microspheres that interact radioactively is usually treated similarly to non-radioactive microspheres. However, the radioactive microsphere always contains one or more radio-nuclides in addition to the matrix material that gives the microsphere its targeting capabilities in a particular tissue or organ. Radioactive microspheres can deliver high radiation doses to a particular area in small quantities as well without harming the surrounding natural tissue. [13, 14]

5] Polymeric microspheres:

The different types of polymeric microspheres can be classified on the basis of biodegradable and non-biodegradable polymers into:

I] Biodegradable polymeric microspheres:

Because natural polymers like starch are biodegradable, biocompatible, and bioadhesive, they are employed. When biodegradable polymers come into touch with mucous membranes, they stay longer because of their high degree of swelling property with aqueous medium, which causes gel to form. The polymer concentration and the sustained release pattern regulate the drug's release rate and extent. The primary disadvantage is the complexity and difficulty in controlling drug release associated with the drug loading efficiency of biodegradable microspheres in clinical settings. On the other hand, they offer a broad range of applications in microsphere-based therapy[15].

II] Synthetic polymeric microspheres:

Synthetic polymeric microspheres are widely used in clinical application, but the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage[16].

Method of Preparation:

Certain requirements should be met when preparing microspheres.

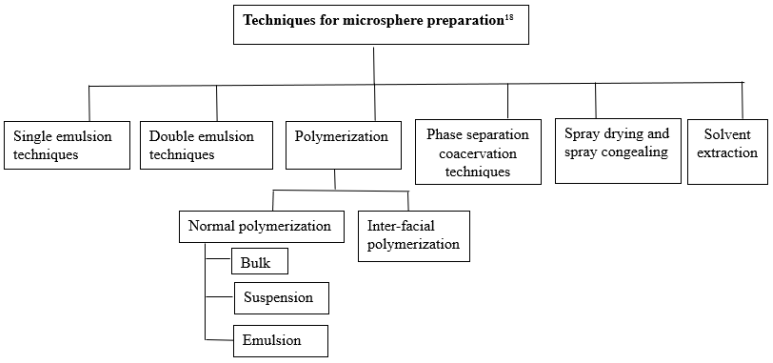
1]The ability to incorporate drug at reasonable concentrations

2] stability of the preparation following synthesis with a clinically acceptable shelf-life

3] Controllable particle size and dispensability in aqueous vehicles for injection

4] Good control over the release of the active agent over an extended period of time

5] Biocompatibility with controlled biodegradability, and susceptibility to chemical modification are the six factors that need to be considered.[17].



1] Single emulsion technique:

There are several natural polymers for ex-carbohydrates and proteins that act as microparticulate carriers and are prepared by single emulsion technique. In which the natural polymers are dissolved or dispersed in the non-aqueous medium e.g. oil. In next step, cross linking is carried out by either of two following methods;

I] Cross linking by heat:

Cross linking by heat is carried out by adding the dispersion, to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs.

II] Chemical cross linking:

Chemical cross liking is done with the help of agents such as glutraldehyde, Formaldehyde, terephthaloyl chloride, diacid chloride, etc. This method suffers from disadvantage of excessive exposure of active ingredients to chemicals if added at the time of preparation, chitosan solution (in acetic acid) by adding to liquid paraffin containing a surfactant resulting in the formation of w/o emulsion. Metformin hydrochloride microsphere are prepared by using glutaraldehyde 25% solution as a cross linking agent[19].

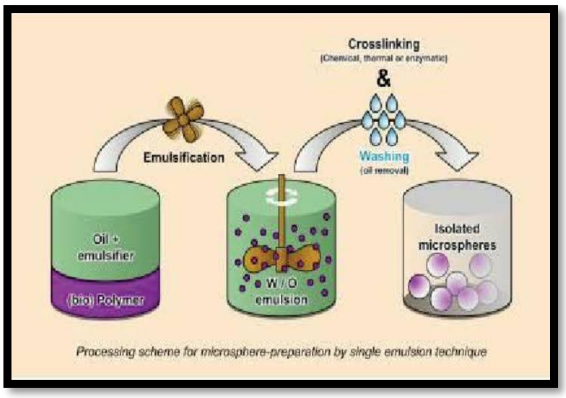


Fig 1: Single emulsion technique

2] Double emulsion technique:

The method of double emulsion solvent evaporation/extraction is ideal for incorporating water-soluble drugs, peptides, proteins, and vaccines into microspheres. It involves dispersing a protein solution in a lipophilic organic continuous phase, homogenizing it, and adding polyvinyl alcohol to form a double emulsion. The emulsion is then removed by solvent evaporation or extraction, resulting in solid microspheres. This method has been successfully used to incorporate hydrophilic drugs, vaccines, proteins/peptides, and conventional molecules.

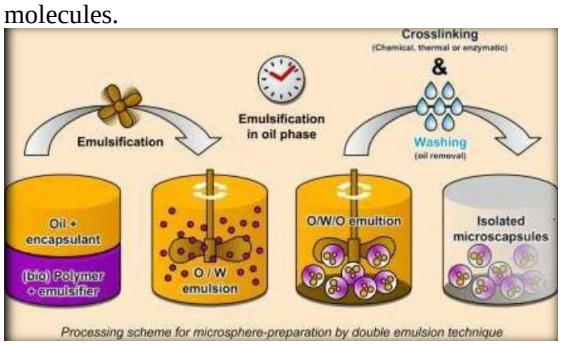


Fig 2: Double emulsion technique

3] Polymerization technique:

The polymerization techniques used for the preparation of the microspheres are mainly classified as :

I] Normal polymerization

II] Interfacial polymerization

I] Normal polymerization:

1] Bulk polymerization:

To start the polymerization and complete the process, a monomer or a combination of monomer and initiator is often heated. To help or quicken the pace of the reaction, the catalyst or initiator is introduced to the reaction mixture. The resulting polymer can be broken up into microspheres or molded. Adsorptive drug loading or drug addition during the polymerization process are two possible approaches for drug loading.

2] The suspension polymerization:

Heating the monomer or combination of monomers containing active ingredients (drugs) as droplets dispersing in a continuous aqueous phase is how it is done. Other additives and an initiator could also be included in the droplets.

3] The emulsion polymerization:

Nonetheless, is distinct from suspension polymerization since the initiator is present in the aqueous phase and diffuses to the micelle or emulsion globule surface afterwards[17].

II] Interfacial polymerization:

The interfacial polymerization process involves two reactive monomers, one dissolved in the continuous phase and the other distributed there. The second monomer is emulsified during the continuous phase, often aqueous. The monomers diffuse quickly and polymerize quickly at the interface. The polymer's solubleness in the emulsion droplet can affect the carrier form. Temperature, vehicle composition, monomer concentration, and reactivity can affect polymerization. Particle size can be regulated by adjusting the size of dispersed phase droplets or globules. Controlling the polymerization process requires maintaining monomer concentration.

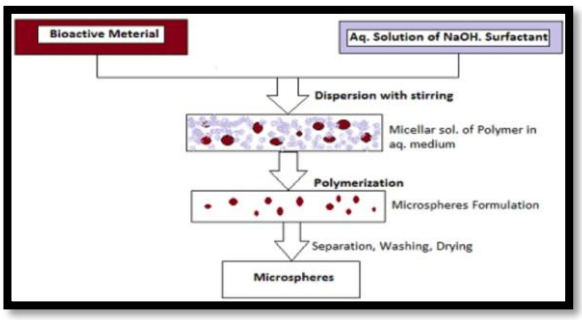


Fig 3: Polymerization technique

4] Phase separation coacervation technique:

specifically made to prepare the reservoir type of the system, that is, to encapsulate pharmaceuticals that are soluble in water, like as proteins and peptides, and medications that are hydrophobic, like steroids. The medication or protein in a matrix-type device is soluble in the polymer phase. The method works on the basis of reducing the polymer's solubility in the organic phase to influence the development of the coacervates, a polymer-rich phase. The creation of two phases, one of which is the supernatant depleted of polymer, can be caused by adding a third component to the system, therefore exacerbating the situation. This method involves dissolving the polymer in an appropriate solvent first, and then dispersing the drug if hydrophilic in an aqueous solution or if hydrophobic by dissolving it in the polymer solution itself. Next, phase separation is achieved by adjusting the conditions of the solution[21,18.]

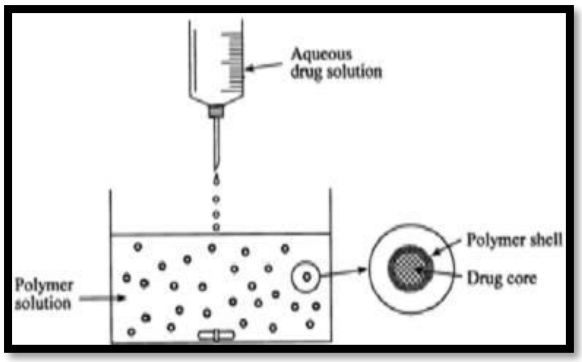


Fig 4: Phase separation coacervation technique

5] Spray drying and spray congealing:

Spray drying process concept The two processes are spray drying and spray congealing, and they rely on whether the solvent is removed or the solution cools down. The fundamental process of spray drying is evaporation, while the mechanism of spray congealing is a phase inversion from a liquid to a solid. With the exception of energy flow, both procedures are comparable. The most used industrial method for drying and forming particles is spray drying. Because of this, spray drying is the best method when the final product needs to meet exacting requirements for bulk density, particle shape, residual moisture content, and particle size distribution.

Principle: Three steps involved in spray drying :

I] Atomization: the transformation of a liquid stream into tiny droplets.

II] Mixing: this process includes directing a hot gas stream through spray droplets, causing liquids to evaporate and leaving behind dry particles.

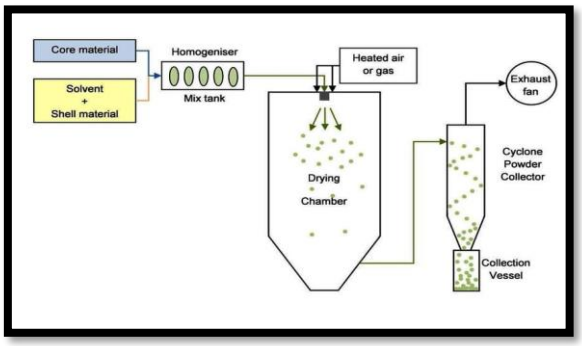
III] Dry: The powder is collected after being dried and removed from the gas stream.

The method of double emulsion solvent evaporation/extraction is ideal for incorporating water-soluble drugs, peptides, proteins, and vaccines into microspheres. It involves dispersing a protein solution in a lipophilic organic continuous phase, homogenizing it, and adding polyvinyl alcohol to form a double emulsion. The emulsion is then removed by solvent evaporation or extraction, resulting in solid microspheres. This method has been successfully used to incorporate hydrophilic drugs, vaccines, proteins/peptides, and conventional molecules.

Fig 5: Spray drying and spray congealing

6] Solvent extraction:

For the emulsion to develop between the polymer solution and an immiscible continuous phase in both the non-aqueous (w/o) and aqueous (o/w) phases. In their 2000 study, Bogataj et al. used the evaporation technique to create microspheres utilizing liquid paraffin and acetone as solvents. After dispersing the medication solution (in acetone) in chitosan solution, the combination was emulsified in liquid paraffin and agitated. The microsphere suspension underwent filtration, washing, and drying. Additionally, magnesium stearate was used as an agglomeration-preventing agent. The findings demonstrated that as the amount of magnesium stearate utilized to prepare the microspheres increased, the average particle size dropped.



examined the comparison between hyaluronic acid and gelatin microcapsules made by complicated coacervation and mucoadhesive microspheres of hyaluronic acid, chitosan glutamate, and a mixture of the two made by solvent evaporation[24,25].

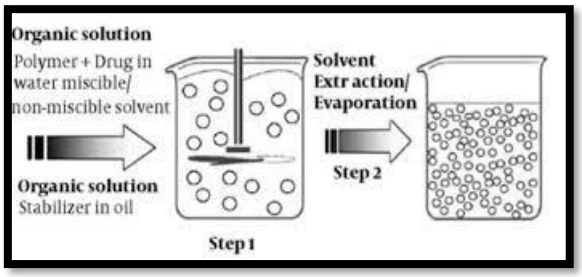


Fig 6: Solvent Extraction Technique

Evaluation of Microspheres:

1] Particle size and shape:

Scanning electron microscopy (SEM) and conventional light microscopy (LM) are commonly used to study microparticles, revealing their external structure and form. LM allows control over coating settings, while SEM offers higher resolution. Conflocal fluorescence microscopy characterizes multiple-walled microspheres, while laser light scattering and multisize Coulter counter can also be used[26].

2] Electron spectroscopy for chemical analysis:

Conflocal fluorescence microscopy is used to evaluate the structural properties of multiple walled microspheres. Apart from instrumental methods, the size, shape, and morphology of the microspheres may be evaluated using multisize Coulter counter and laser light scattering[27]

3] Attenuated total reflectance Fourier Transform-Infrared Spectroscopy:

The carrier system's polymeric matrix degradation is assessed using FT-IR. Alternate total reflectance (ATR) is used to measure the surface of the microspheres. Infrared spectra of the sample's surface material were mostly obtained by many

reflections of the IR beam that passed through the ATR cell. ATR-FTIR analysis yields surface composition information about the microspheres based on circumstances and production processes.

4] Density determination:

A multivolume pycnometer can be used to measure the density of microspheres. The multi volume pyrometer is filled with a precisely weighed sample that is placed in a cup. The chamber is filled with constant pressure helium, which is then allowed to expand. The pressure inside the chamber decreases as a result of this expansion. There are two sequential pressure decrease readings recorded, each at a different beginning pressure. Two pressure readings are used to calculate the volume and, consequently, the density of microsphere carriers[28].

5] Isoelectric point:

An instrument called a micro electrophoresis is used to evaluate the electrophoretic mobility of microspheres in order to identify their isoelectric point. Particle movement over a distance of 1 mm is timed to determine the mean velocity at various pH levels between 3 and 10. This information may be used to calculate the particle's electrical mobility. The surface contained charge, ionisable behavior, or ion absorption nature of the microspheres can all be connected to the electrophoretic mobility[27].

6] Drug entrapment efficiency:

A measured quantity of microspheres are removed and broken apart. then, with the aid of a stirrer, dissolved in buffer solution and filtered. Using a calibration curve, the filtrate is tested at a certain wavelength using a UV spectrophotometer.

Drug Entrapment efficiency =

$$\frac{\text{Actual weight of microspheres}}{\text{Theoretical wt. of drug and polymer}} \times 100$$

7] Percentage yield:

It is computed by dividing the total weight of the medicine and polymer needed to make each batch by the weight of microspheres that were obtained from it, then multiplying the result by 100

8] Swelling index:

It is ascertained by measuring the degree of microsphere swelling in a certain solvent. Five milligrams of dried microspheres are placed into five milliliters of buffer solution and left overnight in a measuring cylinder to reach the equilibrium swelling degree of the microspheres. It is computed using the provided formula.

Swelling index =

$$\frac{\text{Mass of swollen microspheres} - \text{Mass of dried microspheres}}{\text{Mass of dried microspheres}} \times 100$$

9] In vitro methods:

This technique makes it possible to determine a drug's permeability across a membrane as well as its release properties. The in vitro approach is used in product development, pharmaceutical manufacturing, and other areas as a quality control procedure. It is essential to have sensible and repeatable release data that are generated from settings that are chemically, physically, and hydrodynamically characterized[26, 28].

10] Beaker method:

Using an overhead stirrer, the dosage form is made to stick at the bottom of the beaker holding the medium in this procedure, and the mixture is agitated evenly. The studies' literature uses a range of volumes for the medium (50–500 ml) and stirrer speeds (60–300 rpm).

11] Interface diffusion method:

Dearden and Tomlinson devised this methodology. There are four sections in it. Compartment A, which symbolizes the oral cavity, started out with a suitable amount of medication in a buffer. One octanol is found in compartment B, which represents the buccal membrane, and 0.2M HCl is found in compartment C, which represents bodily fluids. One octanol is also present in compartment D, which symbolizes protein binding. The 1-octanol and aqueous phases are saturated with one another before to use. The samples are taken out and placed back into compartment A using a syringe[18].

13] In vivo method:

Techniques that provide the biological reaction of the organism locally or systemically, as well as those that include direct local assessment of absorption or accumulation of substances at their surface, are used to evaluate the permeability of intact mucosa. A common approach to doing in vivo investigations is the use of animal models and buccal absorption tests [20].

14] Animal models:

Its primary uses include screening a range of chemicals, looking into their mechanisms, and assessing a number of formulations. There are reports on animal models, including pigs, lambs, dogs, and rats. The process usually entails anesthetizing the animal, giving the dosage, taking blood samples at various intervals, and analyzing[22].

15] Buccal absorption test:

For both single- and multi-component medication mixes, it is the most appropriate and trustworthy technique for determining the amount of drug loss from the human oral cavity. The relative significance of drug structure, contact time, initial drug concentration, and solution pH while the drug is retained in the oral cavity have all been effectively investigated using this assay. Human volunteers swirl a 25 ml sample of the test solution for 15 minutes, after which they expect the solution, in order to determine the kinetics of drug absorption. To calculate the amount of medication absorbed, it

is then necessary to calculate the amount of drug that is still present in the ejected volume.[25]

Applications of microspheres:[29,30]

1] Microspheres in vaccine delivery:

A vaccination requires immunity to the microbe or any of its harmful byproducts. The perfect vaccination should meet the following criteria: it should be affordable, safe, easy to use, and effective. Safety and minimizing negative responses are two complicated issues. The technique of administration has a direct bearing on both the safety factor and the level of antibody response. One potential solution to address the shortcomings of traditional vaccines is the use of biodegradable delivery vehicles for parenteral vaccinations. Parenteral (subcutaneous, intramuscular, and intradermal) carriers are of interest because they provide a number of benefits, such as:

- Improved antigen city by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.

2] Targeting using micro particulate carriers:

Targeting, or site-specific medication delivery, is a well-established idea that is receiving a lot of attention. The drug's ability to specifically engage and get access to its target receptors determines how effective it is as a treatment. The drug action is mediated by the employment of a carrier system, which allows the drug to exit the pool in a repeatable, effective, and targeted manner.

3] Monoclonal antibodies facilitated microspheres targeting:

Immunological microspheres are those that are targeted by monoclonal antibodies. Selective targeting to particular places is accomplished using this targeting. The molecules known as monoclonal antibodies are very selective. Monoclonal antibodies (Mabs) with their high specificity can be used to direct microspheres containing bioactive compounds to specified locations. By covalent coupling, mab spheres may be directly linked to the microspheres. The antibodies can be attached to the free aldehyde, amino, or hydroxyl groups on the microspheres' surface. Microspheres can be equipped with maps using any of the following techniques:

- Nonspecific adsorption and specific adsorption
- Direct coupling
- Coupling via reagent

4] Imaging:

The microspheres have been utilized for targeting and have undergone substantial research. Radiolabelled microspheres can be used for imaging a variety of cells, cell lines, tissues, and organs. When it comes to imaging specific areas, the microspheres' variety of particle sizes is crucial. The intravenous particles will become caught in the lung's capillary bed if they are injected somewhere other than the portal vein. This phenomenon is used to create labeled human serum albumin microspheres for scintigraphic imaging of lung tumor masses.

5] Topical porous microspheres:

Porous microspheres with several interconnected gaps ranging in particle size from 5 to 300 µm are known as microsponges. These porous microspheres with active ingredients can be added to formulations like creams, lotions, and powders. These microsponges are used as topical carriers because they can entrap a wide range of active ingredients like emollients, fragrances, essential oils, etc. Microsponges are made of non-collapsible structures with porous surfaces that allow for the regulated release of active substances.

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ASSESSMENT OF PATIENT REPORTED ADVERSE DRUG REACTIONS AND QUALITY OF LIFE IN EPILEPTIC PATIENTS RECEIVING POLYTHERAPY: A HOSPITAL BASED STUDY

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Abstract:

Objectives: Aims to collect and assess the patient reported adverse drug reactions and quality of life in patients receiving anti-epileptic polytherapy.

Methods:A cross-sectional study was carried out in the Psychiatric Out Patients Department (OPD) of Krishna Rajendra Hospital, Mysuru. Patients who were above 18 years of age and willing to participate in the study, met with the specified inclusion criteria were included. The causality of reported ADRs and quality of life were assessed using Naranjo algorithm and QOLIE-10 respectively and analysed.

Results: In a study of 108 subjects, anti-epileptic ADRs were reported by males (50.52%) and females (49.48%). Naranjo scale classified 49% ADRs as probable, 51% as possible. Central nervous system was most affected. Mean quality of life score was 27.17±4.51; 57.4% had good quality of life. No association found in chi-square analysis for age, gender, or number of antiepileptics($p>0.05$).

Conclusion: Anti-epileptic polytherapy's adverse reactions impact mental health and patient quality of life. Rising prevalence underscores the need for vigilant monitoring and prompt reporting to healthcare providers, with clinical pharmacists playing a key role in fostering collaboration for successful epilepsy care.

Keywords: antiepileptics; polytherapy; adverse drug reactions; causality; central nervous system; quality of life; clinical pharmacist

INTRODUCTION

Epilepsy as defined by international league against epilepsy (ILAE), is a characteristic cluster of clinical and electroencephalographic feature, often supported by specific etiological factors. It is a chronic neurological disorder associated with recurrent unprovoked seizures that may involve sensory, motor or autonomic phenomena with or without loss of consciousness.

Globally around 50 million people are affected with epilepsy and in India it is estimated that more than 10 million patients are diagnosed with epilepsy and more than 2 million patients with drug resistant epilepsy.

Disruption of normal homeostasis of the neuron and disturbances in its stability may trigger abnormal neuronal discharge. There are many underlying causes which leads to epilepsy, but in about 50% of the cases the etiology is unknown. According to the ILAE Task Force has developed a criterion which categories the epilepsy causes into six types; genetic, structural, metabolic, infectious, immune and unknown.

Antiepileptic drug (AED) therapy, in epileptic patients are given with four main goals; to eliminate seizure or reduce their frequency to maximum degree, to minimize the occurrence of adverse effects associated with long-term use of AEDs, in either to maintain or

restoring their usual psychological and vocational activities and to maintain normal lifestyle.

Paroxysmal discharges occurring synchronously in a large population of cortical neurons are the characteristic feature of seizure activity. It can be visualized as a sharp wave or a spike on EEG.

Successful therapy is based on evaluating the type of seizure, family history, and extent of associated neurological abnormalities. Initiating AED treatment should be based on the probability of seizure recurrences, the consequences of continuing seizures, and the beneficial and adverse effects of the agent in preventing recurrence. Currently available AEDs occasionally not only fail to control seizure in some patients but also frequently produce adverse effects that ranges from minimal impairment of CNS to death from aplastic anaemia or hepatic failure.

There are numerous bio-psycho-social factors affecting the quality of life in patients with epilepsy especially on polytherapy, patients receiving anti-epileptic polytherapy had are addressed to have higher prevalence of psychiatric comorbidities. It is required to evaluate the development of psychiatric comorbidities in patients receiving anti-epileptic treatment especially on polytherapy. The adverse effects of the ant-epileptic medication and incidence of cognitive impairment is established to have negative impact on quality of life. So, it is important to address the factors such as adverse drug reactions, adverse events and psychiatric comorbidities in epilepsy patients, thus will promote adherence, seizure control, emotional well-being and socio-occupational well-being

MATERIAL AND METHODS

Study design: It is a cross sectional observational study

Study site: Krishna Rajendra Hospital, MMCRI, Mysore.

Study population: An aggregate of 108 study participants with a diagnosis of epilepsy and complying our inclusion criterion from Psychiatry OPD were analysed..

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

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

Inclusion criteria:

- Patients with epilepsy aged 18 yrs. Or older,
- Patients who are willing to participate and patients receiving anti-epileptic multi-drug regimen for at least one year were included

Exclusion criteria:

- Patients with significant disability, major psychiatry disorders, substance abuse, severe medical comorbidity confounding the QOL assessment.
- Patients who are pregnant and breast feeding are excluded.
- **Study tools:**

1. .The Informed Consent Form and the Information to participants were initially given to the patient and our objective was explained to the patient prior to each interview with a patient. After approval and signature from the patient, the study was proceeded to collect the demographic details of the patient (Name, Age, Sex, occupation, etc.) and data regarding past and present medical history are collected other data according to the questionnaire and data collection form.
2. Detection of ADRs was performed by face-to-face interview with patients and (or) caretakers at follow up visits and by review of their medical charts containing physical examinations and laboratory findings.
3. MedDRA system organ classification was used to categorize the reported ADRs. The causality relationship between reported ADRs and suspected medication was assessed by Naranjo algorithm. The suspected reactions were informed to concerned physicians and actions take after reaction was also noted.
4. Naranjo scale scoring: Naranjo scale comprises of 10 questions concerning the implicated medication and reaction phenotype. Each answered question has an individual score, which is then totalled to provide a final score that is associated with one of four categories of likelihood that the drug was associated with the reaction (unlikely, possibly, probably, or definitely).Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.
5. QOLIE10 questionnaire scoring: The QOLIE-10 screening questionnaire includes 10 questions. Three questions have opposite response sets, requiring reverse-scoring. The scoring should be calculated so that all positive responses are lower numbers and all negative responses are higher numbers. The total score is the sum of scores for all

questions divided by the number of items answered. Thus, if a patient skipped an item, it is not reflected in the total score. Patients with lowest scores have the least problems.

6. All data obtained from 108 patients were entered and analysed using MS excel software. Data were presented in frequency and percentage. Chi-square test was used in analysis and P ≤ 0.05 considered as significant.

RESULTS: An aggregate of 108 study participants with a diagnosis of epilepsy and complying our inclusion criterion from Psychiatry OPD were analysed.

DEMOGRAPHICS	NUMBER OF PATIENTS(n)	PERCENTAGE
Gender		
Male	57	52.77%
Female	51	47.23%
Age (in years)		
18-25	11	10.2%
26-44	56	51.9%
45-70	41	37.9%
Marital status		
Married	76	70.37%
Unmarried	32	29.62%
Education		
Educated	20	18.51%
Uneducated	88	81.48%
Occupation		
Employed	58	53.70%
Unemployed	50	46.29%

Table 1: Demographics of the study population

Comorbidities: In the included study population, the patients were presented with psychiatric related comorbid conditions and were reported as following, depression being the common condition 11.11% (n=12), followed by anxiety 7.61% (n=8) and psychosis 6.48% (n=7). Majority of patients, 75% (n=81) had no reports of psychiatric illness.

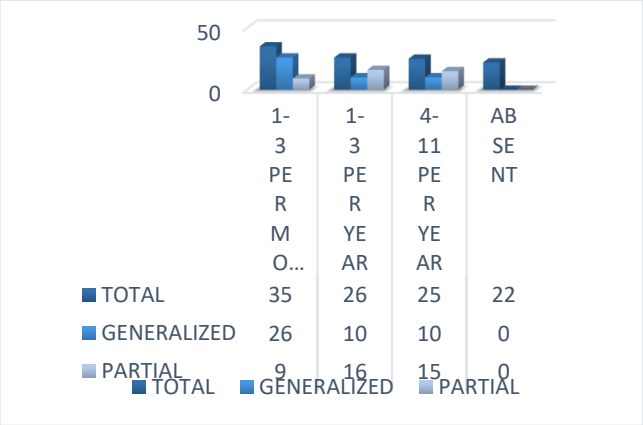

Fig 1: Distribution of Psychiatric illness as comorbidities in study population taking anti-epileptic polytherapy

Types and Frequency of seizures in the study population:

The study conducted among n=108 patients having epilepsy showed that 79.62% (n=86) were presented with epilepsy with ongoing medications, and only 20.37%(n=22) were free from epilepsy and were continuing the medications. The study focused on to the type of seizures and were broadly classified, and showed result, as patients with generalized seizure were about 53.48% (n=46) and partial seizures were 46.51% (n=40). The frequency of epileptic attacks were obtained and were found to be as follow, number of patients having seizure incidence of 1-3 per month were n=35 and within that n=26 (69.44%) were generalized and n=9 (25%) were partial type of seizures, and seizure incidence of 1-3 per year were n=26 and within that n=10 (38.46%) were identified as generalised and n=16(61.53%) as partial seizures, followed by n=25 were having seizure frequency of 4-11 per year were n=10 (40%) identified as generalized and n=15 (60%) as partial seizures

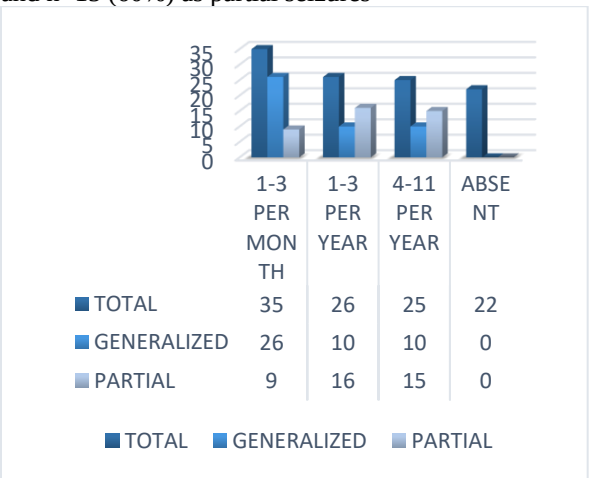

Figure2: Distribution of seizure frequency and type of seizure among the patients

Adverse Drug Reactions

The study conducted among n=108 participants, who were best fit for the inclusion criterion resulted in estimation of 249 ADRs in total during the Psychiatry OPD visit. It was found that among the n=108 participants 89.81% (n=97) were reporting that they were experiencing ADRs and only 10.18% (n=11) were reported to have no ADRs.Among the reported ADRs about 127 ADRs were classified as possible and 122 ADRs as probable according to the use of Naranjo Scale of causality assessment.

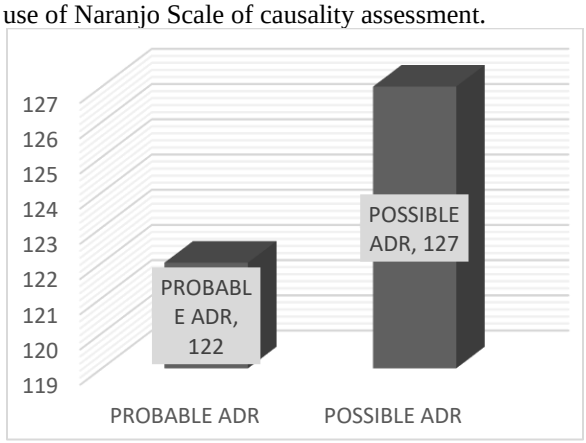

Figure3 :Distribution reported ADRs according to Naranjo scale

It is understood that male 53.41% (n=133) experienced a greater number of ADRs compared to female 46.58% (n=116). From the table, gastric irritation (8.03%) is more prevalent ADR among the patient taking anti-epileptic drugs.

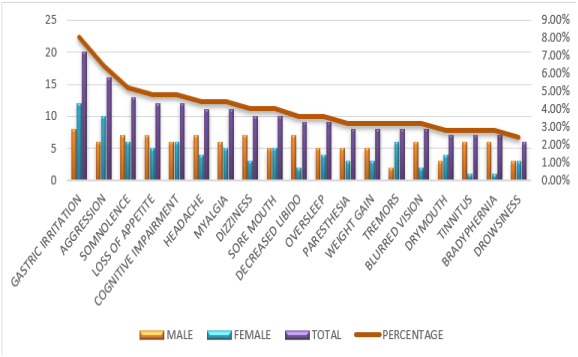

Figure 4:Distribution of ADRs on gender basis and percentage of each ADRs against total reported ADRs (1)

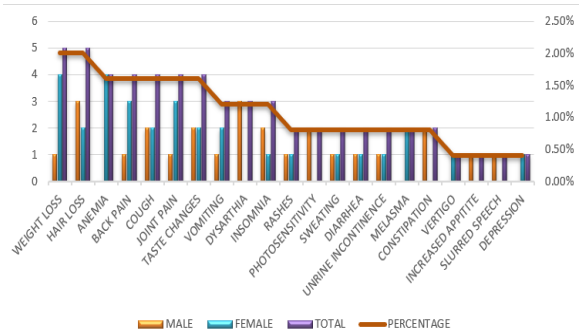

Figure 5: Distribution of ADRs on gender basis and percentage of each ADRs against total reported ADRs (2)

Adverse drug reactions classified under MedDRA System Organ Classification

The number of total ADRs were reported n=249, and the same was classified according to the MedRA system organ classification, to understand the reported ADRs affects which part of organ system by the intake of anti-epileptic polytherapy. It was found that ADRs reported were more in number under the CNS related disorders 30.92% (n=77), followed by GI disorders 19.27% (n=48) .

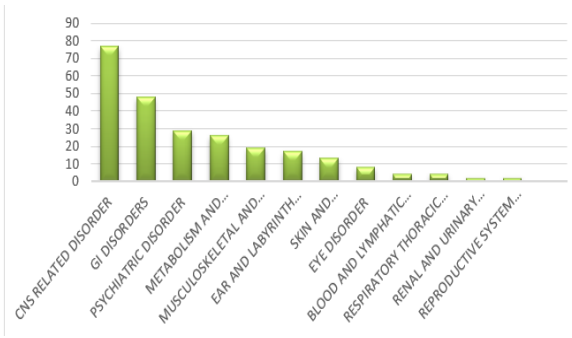

Figure 6:Distribution of ADRs according to MEdDRA System Organ Classification

Risk Factor Analysis of Adverse Drug Reaction

The probable risk factor for developing ADRs such as Gender, Age, Regimen were considered for the risk factor analysis and the result are shown in following table.

Factors	Number (n)	Chi-square value	P-value
Gender Male Female	 57 51	1.955739451	0.16197
Age ≤45 >45	 71 37	0.6815576	0.4090509
Regimen ≤3 Drugs >3 Drugs	 74 34	0.100575	0.751141

table 2: Details of factors influencing adverse drug reaction Statistically significance level p≤0.05
(*) indicates results are significant

Quality of life of patients having epilepsy involved in the study

The factors affecting the quality of life of the study participants having epilepsy is listed in table 5 and their respective QoL scores are being listed. The quality of life of the participants were assessed by QOLIE-10 questionnaire and the result obtained showed that mean score of QoL was found to be 27.17 ± 4.51. For patients having less than or equal to the mean value then, they are said to have good quality of life and those who are having greater than the mean value, poor quality of life. Broadly, among n=108 study participants, 57.4% (n=62) were having good quality of life and the remaining 42.6% (n=46) were having poor quality of life. Quality of life score each variable were carried out and are listed on table6.

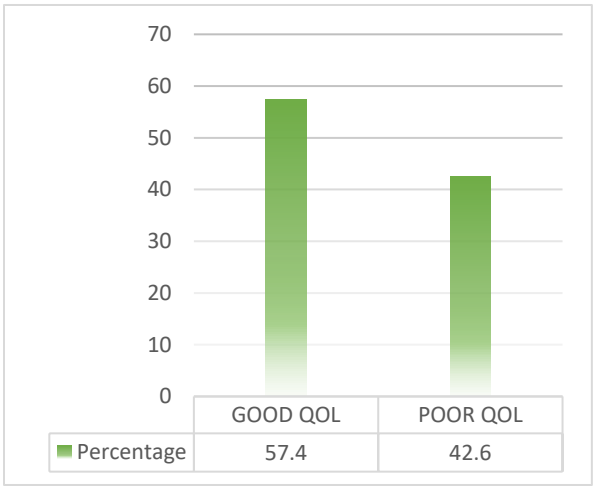

Figure7: Graph depicting percentage of quality of life in study population

VARIABLES	CHARACTERISTICS	NUMBER OF PATIENTS (n)	TOTAL QOL SCORE MEAN (SD)
GENDER	MALE	57	26.75 ± (4.63)
	FEMALE	51	27.64 ± (4.37)
AGE	18-36	42	27.23 ± (4.50)
	37-54	51	27.31 ± (4.55)
	55-72	15	26.53 ± (4.65)
EDUCATION	EDUCATED	20	26.88 ± (5.33)
	UNEDUCATED	88	28.02 ± (4.35)
OCCUPATION	EMPLOYED	58	26.10 ± (4.31)
	UNEMPLOYED	50	28.42 ± (4.46)
PSYCHIATRIC ILLNESS	ANXIETY	8	31.70 ± (4.24)
	DEPRESSION	12	32.00 ± (2.95)
	PSYCHOSIS	7	29.80 ± (2.28)
	NO PSYCHIATRIC ILLNESS	81	25.74 ± (3.90)
FREQUENCY OF ILLNESS	1-3 PER MONTH	35	29.71 ± (3.61)
	1-3 PER YEAR	26	27.98 ± (4.46)
	4-11 PER YEAR	25	26.89 ± (3.29)
	ABSENT	22	22.68 ± (3.90)
ONSET OF ILLNESS	≤3YRS	6	28.33 ± (4.17)
	≤5YRS	34	27.52 ± (4.22)
	≤10YRS	68	26.89 ± (4.71)
ADVERSE DRUG REACTION	ADR PRESENT	97	27.73 ± (4.27)
	ADR ABSENT	11	22.27 ± (3.60)

Table 3: Factors affecting the quality of life according to demographics and current clinical characteristics and their respective QoL score

DISCUSSION

Characteristic of study population

Data regarding socio demographic details of patients in our study showed that 52.8 % were male and 47.2% were female. The male predominance in our study was also found by similar study conducted by Mohammed BisetAyalew et alreporting 61 % male and 39% female and KeerthiJayelakshmi et al reporting 60% male and 40% female.

It was observed from our study that majority of the patients around 51.9% were between the age category 26-44 years which was analogous with study conducted by Esileman et al that reported 42.4 % of patients falling in category of 26-44 years.

Demographic of patients experiencing adverse drug reactions

In this study, 249 adverse drug reactions related to antiepileptics were reported from 97 patients out of 108 patients. The overall ADR rate was 89.8% which coincides with the similar study conducted by Yanru Duet al reported more than 50% of total ADR. An average of 2.56 ADRs occurred per patient with an ADR which is comparable to study conducted by

Yanru Du et al and Sachin Kumar et al reporting 2.79 ADRs per PWE 1.96 ADRs per PWE respectively.
The data also shows that male reported 50.52% of ADRs and female shows 49.48% of ADRs which is comparable to study conducted by MudasilMaqbool et al reported male showing 60.9% of ADRs and female showing 39.1% of ADR and Sachin Kumar et al reported male showing 61.5% of ADR and female showing 38.5% of ADR.
The result of chi square implicated that that there was no statistically significant relationship between the gender and presence and absence of ADRs (p=0.86). This coincides with study conducted by Keerthi Jayelakshmi et al.
Causality assessment of reported ADRs
Causality assessment by the Naranjo algorithm revealed that 49%ADRs were probable and 51%ADRs were possible. Similar finding was observed from study conducted by SohaNamazi et al reporting 42.75 % probable ADRs and 57.25% possible ADRs.
Categorization of ADR
According to the system-organ classification of AED-related adverse reactions the most common involved system is central nervous system (30.92%) followed by gastro intestinal disorder (19.28%) which show similar result from earlier study conducted by B M Gajjar et al reporting 60.71% of ADRs related to CNS followed by 60.71%ADRrelated to CNS, KeerthiJayelakshmi et alreporting42.85% of ADRs related to CNS and SohaNamazi et alreporting 44.08% CNS related ADRs.
Psychiatric comorbidity among study subjects
The occurrence of depression (11.11%) was more followed by anxiety(7.40%) and psychosis (6.48%)among 108 study subjects. These finding are consistent with findings of study conducted by JagritiYadav et al reporting most patients receiving antiepileptic polytherapy with major depressive disorder(32%) followed by anxiety spectrum disorders(n=28%) and suicidality (18%). The higher risk of depressive symptoms in patients with antiepileptic polytherapy can be associated with mechanism of antiseizure medications. The study conducted by Carlos Artega Rodriguez et al also reported that most frequent disorder found were depression disorder (22.8%), anxiety disorder (17.8%), psychosis (10%), bipolar affective disorder (8.5%) and psychogenic non epileptic seizure (5%).
Assessment of quality of life
The mean overall quality of life score of patients in this study is 27.17 ± 4.51. This result is in line with the study conducted by EsilemanAbdelaMuche et al which reported a mean quality of life of 19.86 and study conducted by JagritiYadav et al reported mean quality of life of 37.58±18.45.

CONCLUSION

Adverse reactions have significant safety concerns and they cause treatment failure due to impaired adherence to medication and thus effects the quality of life of patients. The prevalence of adverse drug reactions tends to increase when individuals with epilepsy are on antiepileptic polytherapy highlighting the need for careful monitoring and management. Indeed, in the context of managing epilepsy, altering medications or adjusting dosages can be challenging due to seizure recurrence. Therefore, it becomes essential to promptly report any adverse drug reactions to healthcare providers. Early reporting allows for effective management of ADRs through symptomatic treatment and adjustments that minimize the impact on overall quality of life of patient.

In tertiary hospital clinics, where time with doctors is limited, clinical pharmacists' step in as valuable allies in educating and ensuring compliance among epilepsy patients by conveying vital information about epilepsy, treatment option and potential adverse drug reactions in a concise manner.

ADR management in antiepileptic polytherapy is a delicate task where collaboration between patients, clinical pharmacists and healthcare professionals is pivotal for successful epilepsy care.

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FORMULATIONS AND EVALUATION OF HERBAL WET FACE PACK

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ABSTRACT :- The objective of this work to formulate and evaluate herbal wet face pack by using ingredients like turmeric, Sandal Wood, Rose Petal Powder, Nutmeg Powder, Orange Peel powder etc. This ingredients are weigh accurately and mixed geometrically to uniform formulations and then evaluated for following parameters like Physicochemical properties, Organoleptic parameter, Irritancy test along with stability formulations. We can formulate herbal wet face pack by using easily available ingredients. After evaluation we analyze that good properties for face pack free from skin irritation. The main advantage of herbal products that is pure does not have any adverse effects on human body . The face pack has natural skin lightning properties can easily prepared at home. Herbal face pack provide nutrients to the skin.

KEY WORD :-
Herbal face pack, Natural, Skin , Formulation, Evaluation

INTRODUCTION:-

Currently a days, The Herbs are widely utilized as remedial vendors because herbs are handily convenient at slightly costly. [1] Cosmetics are commercially accessible products that are utilized to enhance the aspect of the skin by effort of cleaning, beautifying, improving and attractiveness. [2] This herbal paste massaged on face to treat acne, pimples, scars ,mask and pigments. [3] Face Pack utilized in ayurveda benefits to decrease wrinkles, pimples, acne and dark circles. [4] Natural face packs are slightly improving fresh simple to utilize. Impact of face pack commonly short and for normal shine it should be utilized 2-3 times a week. [5] The natural face pack include some essential vitamin that are needed for the health and glowing skin.[4] Cosmetic are commercially usable product that are utilized to enhance character of the skin by effort of cleansing, beautifying and to manage them.[3]

MATERIAL AND METHODS :-

MATERIALS :-

1.Multani mitti (Calcium bentonite) :-

Synonyms:- Multan clay

Description:- Colour :- White
Odour :- Pleasant
Taste. :- Pleasant [6]

Chemical Constituent :- Montmorillonite [(Mg.Ca) O.Al_2O_3.5SiO_2.nH_2O] , Kaolinite.[7]

Uses :-1. Nourishes skin , Reduce oiliness , Remove blackheads . [6]

2. Multani mitti benefit the skin by several ways like decreasing pore sizes, eliminating blackheads, Whiteheads fading freckles, relieving sunburns , purification skin , enhancing blood circulation, comlexation , decreasing acne, scars and provides a shining outcome to skin as they include healthy nutrients. [8]

2. Turmeric (Curcuma longa) :-

Synonyms:- Curcuma longa, Indian saffron

Description:- Colour :- yellowish orange to orange
Odour :- Aromatic
Taste :- Bitter

Chemical Constituent :- Volatile Oil, resin , sufficient zingiberaceous ,Turmerone , zingiberene , borneol , caprylic acid .[9]

Uses :- 1. Turmeric is utilized as a antiseptic, expentorant a gravies or spice and coloring agent. [11]

3. Aloe Vera (Aloe barbadensis) :-

Synonyms:- Aloe

Family :- Liliaceae

Description :- Colour :- It is shady brown, brownish black or black in colour.
Odour :- Characteristics
Taste:- Intensely bitter and disgusting

Chemical Constituents :- Barbolin , resin and aloe – emodin. Isobarbalin is living in Curaco and Caps aloes.

Uses:- 1. It is utilized as a irritant purgative.

4.Sandalwood (Santalum alba) :-

Synonym:- Yellow Sandal Wood, Lignum santali

Family:- Santalaceae

Description :- Colour**:-** Yellowish or pale reddish
Odour:- Strong and fragrant
Taste :- Slightly bitter

Chemical Constituent:- alpha – santol and beta - santol . The oil further includes an aldehydes santalal , Santene, santenone , teresantol.

Uses:- 1. The Sandal wood oil is utilized for symptomatic therapy of dysurea and in reducing the regularity of micturition noted in tuberculosis of the bladder. [9]
2. It also has anti – acne effects [10]

5. Rose Petal Powder (Rosa indica) :-

Synonyms:- Rosa gallica

Family:- Rosaceae

Chemical Constituent :- It contains volatile oil that contains of citronellol, geranic acid, geraniol, nerol, and additional terpenes .

Uses :- 1. Rose Petal and their preparation attar of rose is utilized in aromatherapy as anti-inflammatory treatment .[12]

2.It can be utilized favorable laxative. Relive discomfort , toothache, stomatitis, Reimbursement the lungs, kidney and liver. It is further reheat of the body , chronic fever, rash and intestinal affection. [13]

6. Nutmeg (Myristica fragrans):-

Synonyms :- Myristica , Nux Moschata

Family:- Myristicaceae

Description :- Colour:- Externally, the kernels are greenish – brown or brown.

Odour:- Strongly aromatic

Taste:- Pungent and aromatic

Chemical Constituent :- The Volatile Oil approximately 4 to 8 % myristicin , elemicin and saffrole . The fatty acid constituent of the fixed oil are myristic (about 60 %) , palmitic , oleic , Lauric and different acids. Geraniol , terpineol , camphene etc are the different constituent of volatile oil of nutmeg .

Uses :- 1. It is utilized as a pungent , stimulant and carminative . It is utilized as a flavoring agent, too.[9]

7. Orange Peel Powder (Citrus Aurantium Dulcis) :-

Synonym :- Orange zest

Family:- Rutaceae

Description :- Colour:- Dark orange red

Odour:- Aromatic

Taste :- Bitter

Chemical Constituent:- Terpenes, Carotenoids, Flavonids etc.

Uses :- 1.Eliminate skin marks and skin spots, Assist to skin whitening. [6]

2. Orange Peel Powder possess anti- oxidative , anti-inflammatory, anticancer, anti- bacterial actions. It is a chemopreventive tool with probable qualities as Dietary anti- cancer agents. [14]

METHODOLOGY :-

1.Collection of all ingredients like Multani mitti, Turmeric, Aloe vera, Sandal Wood, Rose Petal Powder, Nutmeg Powder, Orange Peel powder, etc from local market, Chemical like methyl cellulose, distilled water, Bentonite, Propylene glycol, Sodium lauryl sulphate, Methyl paraben from pharmaceutics department lab from Navsahyadri Institute of Pharmacy college, Pune.

2.Formulation of face pack:- All powders like Multani mitti, Turmeric, Sandal Wood, Rose Petal Powder, Nutmeg Powder, Orange Peel powder are added into distilled water (quantity sufficient) .The bentonite needs to be hydrated in water prior to addition of others ingredients. So bentonite is added. Methyl cellulose added as thickener and Propylene glycol are added as humectants or sifted slowly to avoid the formation of aggregates. Mix until uniform then added the sodium lauryl sulphate as surfactant and methyl paraben as preservative.

3.Evaluation of herbal face pack:-

1.Organoleptic Evaluation:- The Organoleptic parameter contain nature, color, Odor , feel and consistency existed analyzed manually for its physical properties. The smooth and fine character of the face pack. The colour of the face pack was slight yellow. The texture of the formulation was fine . The odor of prepared formulations was pleasant . The Smoothness was smooth of desirable cosmetic formulations.[15]

2.Physicochemical Evaluation:- Physicochemical parameter were specified containing PH determination and moisture content. [16]

PH Determination:- It measurement acidity and alkalinity of products on scale 0-14. PH can be determined by using digital PH Meter. Prepare the solution of face pack probe which deep into this solution .PH of the solution was found to be 7.13.

Moisture content:- Moisture content was determined loss on drying. Weigh accurately 3 gm of sample transfer it into petriplate placed it into hot air oven at 100-108'C. It was weighed until constant weighed determined. [17]

3.Spreadability test :- Spreadability of developed cream was assessed by setting samples in between two slides then reduced to uniform consistency by spotting specified period . The specified period needed to distinguish the two slide was assessed as spreadability . Minor the period brought for the division of the two slides the outcome exhibited favorable spreadability . Spreadability was evaluated by following formula

Spreadability (S) = Weight tied to upper slide (W) × Lenth of glass slide (L) ÷ Time taken to separate slide [18]

4. Stability test:- Stability testing of ready formulations was performed by reserving at various temperature circumstances for the time of one month . The intervals of glass vials formulations reserve at various temperature circumstances like room temperature like 35'C & 40'C were analyzed like physical parameters like color, Odor, PH, Consistency and feel.[19]

5. Antimicrobial evaluation :- Formulation was examined by antibacterial activity against test organisms recently staphylococcus aureus lived achieved from the pharmaceutical Microbiology lab .In this method prepared Nutrient agar by using autoclave method and agar poured into the plate. Formulations ready was varied with necessary amount of distilled water and emitted it in wells. Then inoculate the S.aureus bacteria into plate .Incubate it into incubator for 48 hrs. Then standard conditions of antibacterial activity was analyzed by assessing the diameter of zone of inhibition (mm) including cup size. [20]

RESULTS :-

1.Organoleptic Evaluation:- Face Pack was ready analyzed for Organoleptic parameter indicated in Table no :-1.

Table 1 :- Organoleptic Properties

Sr.No	Parameters	Observations
1.	Appearance	Smooth, Fine
2.	Colour	Slight yellow
3.	Texture	Fine
4.	Odour	Pleasant
5.	Smoothness	Smooth

Physicochemical Evaluation:- Face Pack was analyzed for Physicochemical parameter showed in Table no:-2

Table 2 :- Physicochemical Evaluation

Sr.No	Parameter	Observations
1.	PH	7.13
2.	Moisture content	3.0

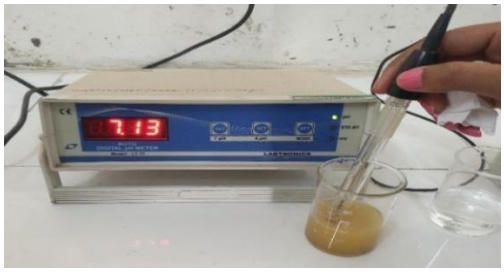
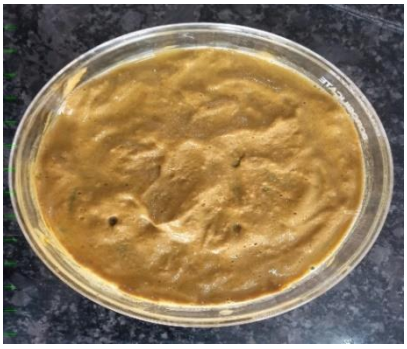
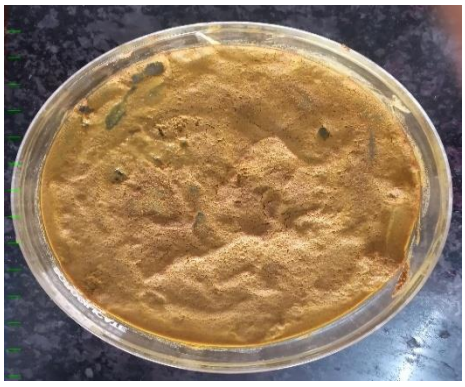


Figure No 1 :- PH Determination



Before



After

Figure No 2 :- Moisture Contents

3. **Spreadability test :-** The results of spreadability test was exhibited in Table :3

Table 3:- Spreadability test

Sr.No	Parameter	Observations
1.	Spreadability test	4.6 g . cm/cm

Figure No 3:- Spreadability test

4. **Stability Studies :-** The results of stability studies test was exhibited in Table :- 4

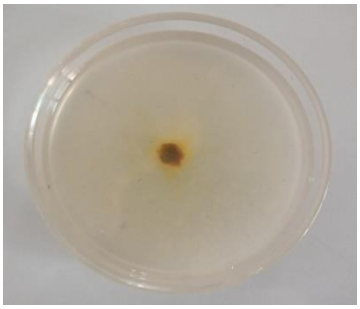
Table 4 :- Parameter of Stability study of formulation

Sr No	Parameter	Observations		
		Room temperature	**35'C**	**40'C**
1.	Colour	No change	No change	No change
2.	Odour	No change	No change	No change
3.	PH	7.13	7.07	6.96
4.	Texture	Fine	Fine	Fine
5.	Smoothness	Smooth	Smooth	Smooth

5. **Antimicrobial evaluation:-** The effects of antimicrobial evaluation was exhibited in Table :5.

Table 5:- Antimicrobial evaluation

Sr.No	Bacteria	Zone of Inhibition formulations (mm)
1.	Staphylococcus aureus	14 mm



Before

After

Figure No 4 :- Antimicrobial Evaluation

DISCUSSION :-

Herbal face pack are used to stimulate blood circulation, rejuvenate the muscle. Helps to maintain elasticity of skin and remove dirt from skin pores . The advantage of Herbal face pack non toxic in nature reduce allergic reactions. The colour of the formulation face pack is slightly-yellow colour had semi-solid consistency. The odor of prepared formulations was pleasant. Smooth and fine characters are present in formulations. Formulation was found to the neutral. The moisture content was within limit. The stability studies indicated little differences in PH formulations was reserved at 40'C and no differences examined at room temperature and 35'C. There was no difference in colour and odour at different mentioned situations of stability test .

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ASSESSMENT OF HEALTH RELATED QUALITY OF LIFE AND ADR IN DIABETIC FOOT PATIENTS UNDERGOING CEFTRIAXONE AND PIPERACILLIN/TAZOBACTAM TREATMENT IN TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: To conduct a comparative study based on HRQoL in diabetic foot patients treated with Ceftriaxone and with Piperacillin/Tazobactam, to identify ADRs associated with these antibiotics.

Methods: A cohort study was conducted in surgery department of KR hospital, Mysuru. SF-36 and Naranjo scale were used respectively to assess HRQOL and causality of ADRs in the study participants.

Results: In our study, patient who received Ceftriaxone showed greater improvement in 6 out of 9 domains, patients who received Piperacillin/Tazobactam showed greater improvement in 3 domains. Diarrhea, anemia and generalized weakness are the common ADRs seen in patients treated with Ceftriaxone. ADRs associated with piperacillin/Tazobactam therapy included anemia, generalized weakness and loss of appetite.

Interpretation and Conclusion: In our study, Ceftriaxone was found to be more effective than Piperacillin/Tazobactam in the aspect of HRQOL in patients with diabetic foot infection. We also observed the presence of significant amount of ADR associated with both drugs. Proper care and support should be provided to the Diabetic foot patients along with suitable medication care.

Keywords: Diabetic foot, HRQoL, Ceftriaxone, Piperacillin/Tazobactam.

INTRODUCTION

Diabetic foot infection is one of the most prevalent and significant complications of diabetes mellitus, which frequently results in hospitalization and disability. In India, 4.54% of people with type 2 diabetes mellitus were discovered to have diabetic foot ulcers. [1]

Poor foot care, peripheral vascular disease, underlying neuropathy, and poor glycemic control are the common causes of developing diabetic foot infection.[2] Microbial invasion into the tissue triggers a host reaction, which then impairs wound healing, leading to a wound infection in diabetic foot infection. can drastically alter innate immune activity, increasing susceptibility. The main risk factor for developing a diabetic foot infection (DFI) is continuing to have a foot wound.[3] The ulcers typically develop in parts of the foot that experience pressure and recurrent stress. The most prevalent infectious organism is Staphylococcus. Diabetic foot infection is also a frequent cause of foot osteomyelitis and lower extremity amputation.[2]

Diabetic foot ulcer is commonly classified according to Wagner's classification of diabetic foot ulcers. According to which the wound is classified as Grade

0, 1, 2, 3, 4, 5.[4] DFI is commonly diagnosed thorough history and physical examination, which is followed by a complete laboratory assessment, microbiology review, vascular assessment and diagnostic imaging. Clinical findings are used to make the diagnosis of a DFI.[5]

The initial treatment for diabetic foot ulcers(DFUs) involves several key approaches such as sharp debridement, offloading, local wound care etc.[6]

Common antibiotic therapy includes Oral cephalosporin, Amoxicillin-clavulanic acid combination, Piperacillin/Tazobactam[7], ampicillin/Sulbactam, if MRSA is suspected, then Linezolid, Clindamycin, Doxycycline, daptomycin. Other antibiotics such as Ciprofloxacin, Levofloxacin, Vancomycin, Linezolid, Daptomycin are also prescribed.[2] In patients with uncontrolled infections or wounds that are not healing, amputation, which is the removal of a nonviable limb, should be taken into consideration. There are numerous amputation levels, including those at the forefoot, midfoot, Syme, below-knee, and above-knee levels.[6]

Piperacillin/Tazobactam is a parenteral antibiotic and provides broad spectrum coverage and is used by clinicians in diabetic foot. A combination of piperacillin and tazobactam, a β-lactam/ β-lactamase inhibitor, has broad-spectrum antibacterial action against both Gramme-positive and negative aerobic and anaerobic bacteria.[7] Ceftriaxone is third-generation cephalosporin with strong activity against the majority of gram-negative bacteria, including the Enterobacteriaceae. Ceftriaxone is stable to betalactamases. It is the only third-generation cephalosporin with such a long half-life.[8]

Studies have shown that diabetic foot ulcers have a negative impact on health-related quality of life (HRQoL). Compared to patients with diabetes, DFU patients had significantly lower HRQoL. Severe HRQoL impairment affects both physical and mental health.[9]

In the Indian population, fluroquinolones, beta-lactam penicillin, and beta-lactam cephalosporin are widely used.[10] Since diabetic foot is commonly treated with empirical therapy, the occurrence of adverse reactions can be expected.

MATERIALS AND METHODS

Study design: Prospective Observational study

Site of the study: The study was conducted in Krishna Rajendra hospital, Mysuru.

Study population: Total 109 patients were included in the study.

Study period: The study was carried out for duration of six months from March 2023 to August 2023.

Department selected for the study: The study was conducted in the department of general surgery, which comprises 18 wards.

Sources of data: All the relevant data were collected from medical and medication record of patients, interviewing patient and caretaker, communicating with concerned physicians and health care professionals and also through telephonic contact with patients and/or physicians if necessary.

Ethical approval for the study: Ethical approval for the study is provided by institutional ethics committee of Mysore Medical College and Research Institute.

Inclusion criteria: Patients who are above 18 years old and suffering with diabetic foot infection, and are treated with ceftriaxone and Piperacillin/ Tazobactum and are willing to participate in the study were included.

Exclusion criteria: Pregnant and breastfeeding women and those diabetic foot patients who did not agree in participating in the study were excluded.

Experimental design: Patients who are suitable for the study were enrolled by obtaining their consent. Patient data inclusive of demographic information such as patient name, age, gender, contact information, other data like medical and medication history, diabetic foot details, DFU grade, treatment etc.. were collected in suitably designed data collection form. To evaluate the quality of life, SF-36 HRQoL questionnaire scale was employed. Patients were interviewed in the beginning of the therapy and later followed up after 10 days to assess the final HRQOL. During the period of the patient's hospital stay, ADR was assessed using causality assessment method-Naranjo scale.

Study tools:

a. Informed consent form: An appropriate ICF was created in both English and Kannada to obtain patient's consent to participate in the study. The patient was fully informed about the study in their regional languages, and their consent was obtained by taking their signature or thumb impression.

b. Data collection form: The form included demographic details of the patient and other data like medical history, medication history, diabetic foot details, relevant laboratory datas, treatment chart of the patient and ADR report.

c. SF-36 HRQOL questionnaire: it is a questionnaire that measures the HRQoL of the patient. It measures the quality of life in 8 scales. The score ranges from 0 to 100 while 0 being minimum and 100 being maximum quality of life.

d. Naranjo scale: Naranjo scale was used to determine the causality of an ADR.

Statistical analysis: Microsoft Excel 2010 was used to conduct the statistical analysis and to evaluate the data. Tables, graphs, means and percentages were used to represent the outcomes. Chi- square test and mean were used in our study.

RESULT

A total of 109 participants from surgery department, K
R hospital were included in the study.

Table 1: Demographics and clinical characteristics of study population

Demographics of the study population			
Demographics		**Number of patients**	**Percentage**
Age	Below 20y	0	0%
	20 – 30y	2	1.83%
	30 – 40y	5	4.58%
	40 – 50y	21	19.26%
	50 – 60y	32	29.35%
	60 – 70y	24	22.01%
	70 – 80y	16	14.67%
	Above 80y	9	8.25%
Gender	Male	86	78.89%
	Female	23	21.11%
Diet	Vegetarian	9	8%
	Mixed	100	92%
Habits	Alcoholic	26	23.85%
	Smoker	41	37.61%
	Pan masala	3	2.7%
	Gutka	2	1.83%
	Other	0	0%
	None	60	55.04%
Clinical characteristics of the participants			
Characteristics		**Number of patients**	**Percentage**
Diabetic history	Newly detected	93	85%
	K/c/o Diabetes	16	15%
Type of diabetes	Type-1 Diabetes mellitus	0	0%
	Type-2 Diabetes mellitus	109	100%
Ulcer grade	Grade – 0	0	0%
	Grade – 1	37	33.9%
	Grade – 2	39	35.7%
	Grade – 3	12	11%
	Grade – 4	9	8.2%
	Grade – 5	12	11%
Amputation	Yes	29	26.60%
	No	80	73.39%
Amputation details	Above knee amputation Below knee amputation Amputation of Foot Disarticulation of Toe/Toes	3 15 3 8	10% 52% 10% 28%

Quality Of Life In Diabetic Foot Patients

Among the 109 patients, 93 patients were interviewed about their quality of life. Among those, 39 were administered with ceftriaxone and 54 were administered with Piperacillin/Tazobactam.

The mean of quality of life in patients taking Ceftriaxone and Piperacillin/Tazobactam was given in the following table.

Table 2: Quality of Life in patients taking Ceftriaxone and Piperacillin/Tazobactam

Mean of quality of life in patients taking ceftriaxone (range= 0-100)	**Mean of quality of life in patients taking Piperacillin / Tazobactam (range= 0-100)**

Domain	Before	After	Domain	Before	After
Physical functioning	7.179	26.794	Physical functioning	8.703	28.71
Role limitations due to physical health	1.282	12.82	Role limitations due to physical health	1.85	11.11
Role limitations due to emotional problems	17.094	69.231	Role limitations due to emotional problems	16.67	65.43
Energy/fatigue	26.538	51.41	Energy/fatigue	28.796	51.85
Emotional well-being	42.153	63.076	Emotional well-being	43.11	64.96
Social functioning	45.512	68.589	Social functioning	47.41	71.06
Pain	16.538	55.833	Pain	20.83	54.26
General health	28.205	52.871	General health	28.15	52.203
Overall	17.948	42.307	Overall	16.67	33.796

The improvement in the quality of life in patients after the administration of drug, i.e., the difference in the before and after in each patient was calculated and their mean was obtained.

Table 3: Comparison of improvement in the health related quality of life (HRQoL) between patients taking Ceftriaxone and Piperacillin/ Tazobactam

Domain (range= 0-100)	Ceftriaxone	Piperacillin/ Tazobactam
Physical functioning	19.61	20.01
Role limitations due to physical health	11.54	11.11
Role limitations due to emotional problems	52.14	48.76
Energy/fatigue	25.51	23.7
Emotional well-being	20.92	21.85
Social functioning	23.07	23.67
Pain	39.29	33.24
General health	24.67	24.05
Overall	24.36	17.13

According to this study, patients who receive Ceftriaxone show greater improvement in 6 out of the total 9 domains. Piperacillin/ Tazobactam show greater improvement in 3 out of total 9 domains. Hence according to our study Ceftriaxone was found to be more effective than Piperacillin/ Tazobactam in the aspect of HRQOL (health related quality of life)of patients with diabetic foot infection.

Adverse Drug Reaction In Diabetic Foot Patients

Among the 109 patients, 41 patients developed ADR on treatment with either ceftriaxone or piperacillin/Tazobactam. In which, 18 patients (43.9%) who developed ADR were taking ceftriaxone and 23 patients (56.09%) who developed ADR were taking piperacillin/Tazobactam.

Table 4: ADR observed in patients taking Ceftriaxone and Piperacillin/Tazobactam

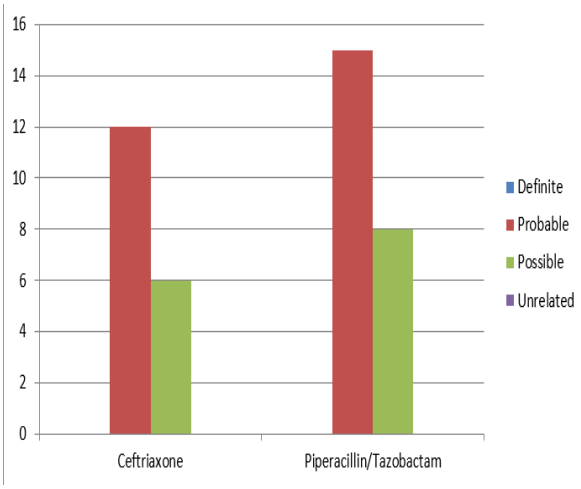
ADR observed in patients taking Ceftriaxone			ADR observed in patients taking Piperacillin/ Tazobactam		
ADR	**Number of Patients**	**Percentage**	**ADR**	**Number of Patients**	**Percentage**
Diarrhoea	5	27.7%	Anemia	14	60%
Anemia	7	38.8%	Generalized weakness	8	34.7%
Generalized weakness	4	22.2%	Loss of appetite	1	4.3%
Thrombocythemia	1	5.5%			
Acute Kidney Injury	1	5.5%			

Causality assessment

Using the Naranjo scale, the causality was assessed by providing a causality score. Among the 18 ADRs detected in ceftriaxone therapy, 12 ADRs were probable and 6 ADRs under possible category, no ADR were seen in definite and unrelated category of causation.

23 ADRs were detected in Piperacillin/ Tazobactam therapy out of which 15 ADRs are under probable category and 8 ADRs under possible category, ADR were not seen in definite and unrelated category of causation.

Figure 1: Causality assessment of ADR associated with Ceftriaxone and Piperacillin/Tazobactam



Association of Various Factors with ADR

Various factors that may affect the occurrence of ADR, such as age, gender, diet, habits and diabetic history were considered for the analysis.

Association of various factors influencing ADR in Piperacillin/ Tazobactam					
Factors		**ADRs**		**Chi-square value**	**p-value**
		Yes	**No**		
Age	20- 59	14	22	0.718	0.397
	59- 100	9	22		
Gender	Male	17	32	0.011	0.917
	Female	6	12		
Diet	Vegetarian	0	6	3.44	0.063
	Mixed	23	38		
Habits	With habits	9	14	0.358	0.549
	Without habits	14	30		
Diabetes history	K/C/O Diabetes mellitus	21	36	1.070	0.301
	Newly detected diabetes mellitus	2	8		

Significance was checked by using chi square test. No factors were found significant as the p value for all the factors were greater than 0.05. The result obtained was as the following table

Table 5: Association of various factors influencing ADR in Ceftriaxone

Association of various factors influencing ADR in Ceftriaxone					
Factors		**ADRs**		**Chi-square value**	**p-value**
		Yes	**No**		
Age	20- 59	8	16	2.074	0.15
	59- 100	10	8		
Gender	Male	16	21	0.019	0.89
	Female	2	3		
Diet	Vegetarian	2	1	0.75	0.387
	Mixed	16	23		
Habits	With habits	10	16	0.538	0.463
	Without habits	8	8		
Diabetes history	K/C/O Diabetes mellitus	16	20	0.259	0.61
	Newly detected diabetes mellitus	2	4		

Table 6: Association of various factors influencing ADR in Piperacillin/ Tazobactam

Note: Result is significant when significance level is ≤0.05.

DISCUSSION

Demographic details in our study showed that the mean age of the patients in our study was found to be 57.82 years. Most patients were falling into the age range of 50–60 years (n=32, 29.35%). Majority of the study population were male (78.89%, n= 86) female comprised of 21.11% (n=23). This is similar to a study conducted by **Ravisekhar Gadepalli, Benu Dhawan et al.,** named 'A Clinico-microbiological Study of Diabetic Foot Ulcers in an Indian Tertiary Care Hospital', according to which the mean age of patients in the study was found to be 53.9± 12.1 years. The percentage of male population was 85% in the study subjects.[11]

29 patients in our study had amputation (26.60%), among which below knee amputation was the most common category. Similar findings were found in an article by **Ghosh P, Valia R et al.,** which stated that about 20% of diabetic foot patients requires amputation.[12]

In our study it was found out that, a majority of patients had grade 2 ulcers (35.7%, n= 39). Grade 4 ulcers were found to be rare, affecting only 9 patients (8.2%). Similar results were found in the study conducted by **Jawed Mohammad Akther, Imran ali khan et al.,** According to their study, grade 2 was the commonest ulcer grade comprising 34.5% of the study population and grade 5 was the least common ulcer grade. [13]

In our study, significant improvement is seen in patients taking ceftriaxone and Piperacillin/ Tazobactam. Mean of results in the second observation in patients taking ceftriaxone and Piperacillin/ Tazobactam was found similar to the scores found in an earlier study conducted by **Maria Polikandrioti et al.,** named 'Quality of Life in Diabetic Foot Ulcer: Associated Factors and the Impact of Anxiety/Depression and Adherence to Self-Care'.[14]

In our study, among patients taking Piperacillin/ Tazobactam, a majority of patients developed anemia (n=14, 60%) and 8 patients had generalized weakness (34.7%). This is slightly contradicted to an earlier study conducted by **Will Fry et al.,** which stated that, hematological factors did not change much after the administration of Piperacillin/ Tazobactam, except that five patients developed mild pancytopenia.[15]

23 (34.33%) of the 67 individuals in our study who had taken piperacillin/Tazobactam experienced ADR. Slightly similar result was seen in an earlier study conducted by **Anneke M. Zeillimaker et al.**, on 'Piperacillin/Tazobactum therapy for diabetic foot infection', which stated that 56% of the study population has developed ADR which majorly comprised of nausea, diarrhea, exanthema etc.[16]

CONCLUSION

According to our study, Ceftriaxone was found to be more effective than Piperacillin/ Tazobactam in the aspect of HRQOL (health related quality of life) of patients with diabetic foot infection.

According to our study, the HRQOL of diabetic foot patient was found to be low in overall aspect, which has to be handled properly. Providing proper foot care, wound dressing, management of complication can help in improving the physical aspect of HRQOL of the patient. Doppler test and other vascular investigations play a crucial role in managing diabetic foot infection. Mental and emotional aspect of the quality of life can be improved by providing moral support, counselling and suitable assistance to the patient.

One of the common ADR found in both Ceftriaxone and Piperacillin/Tazobactam was Anemia. It can be managed by constant monitoring of haemoglobin level during treatment period as well as blood cell count. Other common ADRs of ceftriaxone include diarrhea, generalized weakness etc, which should be managed by proper monitoring of the patient along with symptomatic managements.

Along with medication therapy, the patients were advised about the significance of proper foot care and regular dressing. The patients were also advised about preventing the recurrence of diabetic foot by controlling modifiable risk factors like diet, lifestyle, habits (alcohol intake, smoking etc). Health care education and appropriate medication care should be provided to patients with diabetic foot. This study assisted in focusing on common empirically prescribed medications like ceftriaxone and piperacillin/tazobactam and how they affect the quality of life for people with diabetic foot. This study also helped to identify the common ADR associated with the administration of these drugs in the hospital setting.

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