RESEARCH ARTICLE

EFFECTIVENESS OF SAFFRON IN THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE WITH CDR-SB SCORE

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Manuscript Info	Abstract
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Introduction: large levels of glucocorticoids and stress results structural and functional changes in brain and hippocampus, limbic system has akey rolein cognitive functions including learningand memory. Alzheimer's disease (AD) is a chronic neurodegenerative disease.

Objective: the AIM of this study was to assess the efficacy ofsaffron in the treatment of mild to moderate Alzheimer's disease (AD).

Methods: fifty-six patients of 55years old were eligible to participate in this study. The study is a double-blind study of parallel groups of patients with AD.

Results: saffron is effective similar to donepezil in the treatment of mild to moderate AD after 22 weeks. The safety of saffron is comparatively similar like donepezil. The side effects presented with saffron and done pezil groups likely same. The major parameter taken was Alzheimer's disease assessment Scale-cognitive subscale score evaluated with baseline. The safety of saffron was also recorded systemically. Participators were given a capsule saffron 30mg/day(15mg twice daily)or donepezil10mg/day(5mg twice per day).

Conclusion: this studyprovides mainly suggests that possible therapeutic effect of saffron extract at least in short-term treatment of patients with mild-to0moderate Alzheimer's disease.

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Introduction:-
Alzheimer's disease (AD) is the most common form of dementia in the elderly (Tedeschiet.al.2008). this condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increase dapathy, decreased speech function, disorientation, and giant irregularities. AD is the mostwidely known of the degenerative diseases (citron 2004). It is a condition that iscommonly associated with considerable psychological and emotional distress forpatients and their families. It is estimated that 3.5% of the population in the USAbetween the age of 65 and 75 years of age is in at least the initial stage of AD (citron 2004: Tedeschi et al.2008).

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Advancing age is the most common risk factorfor so-called AD with a doubling of risk every 5 years after the age of 65. Femalesare slightly more likely than males to develop Alzheimer's disease (citron 2004; Tedeschietal.2008) deposition of amyloid-β (Aβ) in the brain is a neuronal damage (golde 2005). Although a magic bullet for AD has clear not as yet beenfound, certain medicines offer mode stbene fit, and these may be conveniently divided into three classes, according to whether they may prevent the development of the diseases, retard its progression once it has set in, or offer some symptomatic relief (beckerandgreig 2008; rafiandaisen 2009). The cholinergic hypothesis of AD is based on the decrease in the cholinergic neuro transmission observed in the central corte2x and other areas of the brain (tsuno 2009). The acetylcholinesterase inhibitors such as donepezil, which can increase intra synaptic cholinergic activity by inhibiting the degradation of acetylcholine, are the drugs that have demonstrated in many clinical trials beneficial effects on standard measures of cognitive function patients with mild, moderate, or severe AD (tsuno 2009). New studies suggest novel strategies for ADtherapy. The most viable of these at the moment is targeting the disruption of neuro transmitter system. Counter acting over production of amyloid-β (Aβ) isattractive in theory and has spurred the development of secretase inhibitors aswell as active and passive immunization techniques. Nevertheless, the present drugs effects are quit elimited (beckerandgreig2008; rafiiandaisen 2009).

Herbal medicine is still the mainstay of about 75-80% of world population, mainlyin the developing countries, for primary health care because of better cultureacceptability, better compatibility with the human body, and lesser side effects (Ernst 2006). However, the last 2 decade has seen a major increase in their use inthe developed world (mantel et al. 2002; izzo and capasso 2006). Preliminary clinical evidence indicates that some herbal medicines can ameliorate learning and memory in patients suffering from mild-to-moderate AD (wake et.al 2000; akhondzadeh and abbasi 2006). Potential beneficial actions exerted by the active ingredients of the seherbs are not limited to the inhibition of cholinesterase inhibitors and include the modification of Aβ processing, protection against apoptosis and oxidative stress, and anti-inflammatory effects (wake et al. 2000; akhondzadhe and abbasai 2006). Saffron is the world's most expensive spice and apart from its traditional value asa food additive, recent studies indicate its potential as an anticancer agent andmemory enhancer (abe and saito 2000; abdullaev and Espinosa-aguirre 2004), the value of saffron (dried stigma (the top of the centre part of a flower that receives the pollen which allows it to fromnew seeds) of crocus sativus L.) is determined by the existence of three main secondary metabolite; crocin and itsderivatives which are responsible for colour; picrocrocin which is responsible fortaste; and safranal which is responsible for odour (Schmidt et al. 2007). This plant belongs to the iridaceace family, and as a therapeutically plant, saffron is considered an excellent aid for stomach ailments and an anti spasmodic that helps digestion and increases appetite. It also relives ren2al colic, reduces stomach ache, and relieves tension (akhondzadhe and abbasai 2006; Schmidt et al. 2007). It has been shown that administration of extract of C. sativus L. antagonized ethanol induced memory impairment in the passive avoidance task in the mouse, and the constituent of saffron extract, crocin, prevented ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-depended synaptic plasticity that may under lielearning and memory (sugiura et al. 1995 a,b; akhondzadhe 1999). Inadditional, it has also been reported that crocin counter actedethanol inhibition of N-methyl-D-aspertate receptor-mediated responses in rat hippocampal neurons (abe et al. 1998). Low doses of C. sativus extract antagonised extinction of recognition memory in the object recognition test and scopolamine-induced performance deficits in the passiveavoidance task in rat (pitsikas et al. 2007).

Materials and Methods:-
The study design:
The proposal of this study, 22-week, double-blind study of patients with mild-to moderate Alzheimers disease and was conducted in hospital of Indore, from October 2022 to November 2023.

Measurements:-
The psychometric measure, which includes the MMSE,Clinical Dementia Rating Scale – sums of BoxeS (CDR-SB) is performed to monitor the global cognitive and clinical profile of the subjects.

Interventions:
Patients were randomized to receive capsule of saffron or capsule of donepezilin a 1:1 ratio using a computer-generated code. Donepezil and saffron capsules are visually identical interms of shape and colour. In this double-blind study, patients are randomly assigned to receive capsule saffron 30mg/kg (15mg twice per day) or capsule donepezil 10mg/kg (5mg twice per day) for22-weeks study.

Following the screening phase, a capsule of saffron 15 mg or capsule of donepezil5mg is given for first 4 weeks, after which the dose is increased to two capsules ofsaffronordonepezilperdayfortherestofthestudy.

Preparation of capsule of saffron
The saffron used in this study is donated by Sri Lalitha Mahaa Tripura Sundar iDevi Nursery (Tirupati, Andhra Pradesh). The saffron capsules used in this study will prepared as follows: 120g of dried and milled C. sativus L. stigma will extracted with 1800 mL ethanol (80%) by percolation procedure in three steps, and the ntheethanol extract will be dried by evaporation at a temperature of 35– 40°C. Each capsule contained dried extract of saffron 15mg) , lactose (filler), magnesium stearate (lubricant), and so diumstarch glycolate (disintegrate). The most important compounds in saffron are crocin, picrocrocin, and safranal. Drugs amples are evaluated by safranal and crocinvalues by means of a spectro photometric method. Safranal and crocin values are were expressed direct reading of the absorbance at about 330 and 440 nm, respectively. Each capsule had 0.13-0.15mg safranal and1.65-1.75mg crocin.

Safety evaluation:
All adverse events were report or observed, had record at each visit. Routine physical examination was conducted at each clinical visit. Complete physical examinations, including12 lead electro cardiogram recordings, was conducted at weeks 0,8, and22.
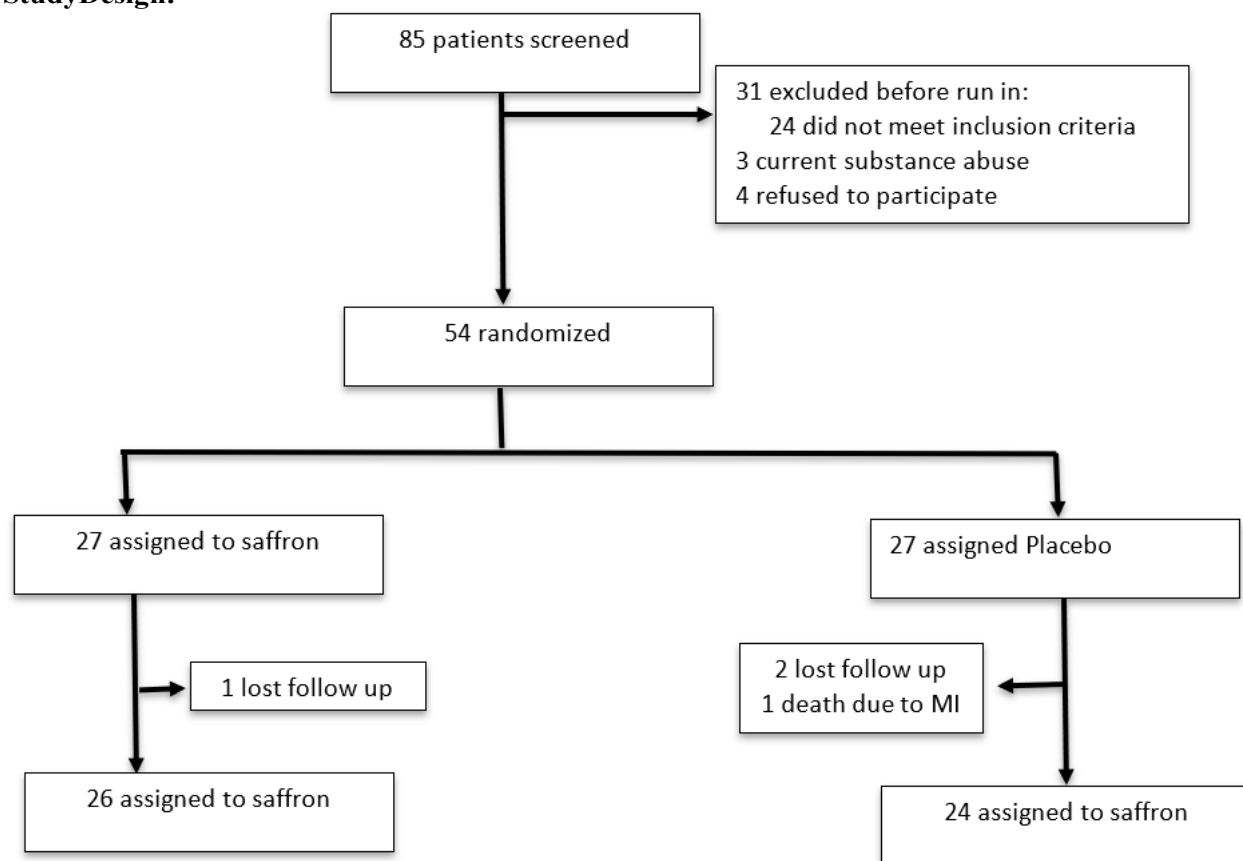
Samplesizecalculations:
On the basis of previous literature prevalence statistics on mean CDR-SB witha standard deviation of 3, a power of 90%, a two-sided significance level of 0.05, and an attrition rate of 25%. Therefore, a sample size of 150 will be calculated foreach group. IBM SPSS Statistic 20 (IBM Corporation, Armonk, NY, USA) will beused for data analysis. All analyses will be based on the intention-to-treat sample and were performed using the last observation carried for ward procedure. General linear model repeated measures analysis was used in order to assess the effect oftime × treatment interaction, considering the treatment group as the between-subject factor and the study measurements as the within-subject variables (time).Independent t test will be used to analyses the 2 groups based on CDR-SB score.The frequency of side effects and the number of patients who remained stable through out this study will be compared between wotrial groups using chi-square test. t. Ap-value of <0.05 was considered statistically significant.

Results:-
From January 2020 to March 2023, 85 patient were screened for the trail, of whom 52 were randomized to either saffron or control capsules. Figure 1 shows the trail profile. There was no variations in baseline property including, age, gender, time of illness and education level (table1).

Efficacy measures CDR-SB
The mean ± SD score of two groups of patients are shown in fig 1 There were no significan tdifferences between the saffron and control groups at the initial week (baseline) on the CDR-SB(t=0.16, df= 50, P= 0.80). The difference between two groups was not significant asused by the effect of group. The character of the two treatment groups was same through out the treatment. At the end point ofthe treatment not significant and compared to baseline were -0.66 ± 0.87 and -0.73 ± 0.85 between the two groups respectively. There was no significant difference was observed on the change of score of the CDR-SB at 22 week collate to base line in the two group (t=0.19,df=50,P=0.79).

StudyDesign:

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                    ┌──────────────────────┐
                    │  85 patients screened │
                    └──────────────────────┘
                               │
                               ├──────────────►  ┌─────────────────────────────────────────┐
                               │                 │ 31 excluded before run in:              │
                               │                 │    24 did not meet inclusion criteria   │
                               │                 │ 3 current substance abuse               │
                               │                 │ 4 refused to participate                │
                               │                 └─────────────────────────────────────────┘
                               ▼
                    ┌──────────────────────┐
                    │    54 randomized      │
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27 assigned to saffron	27 assigned Placebo

1 lost follow up	2 lost follow up 1 death due to MI

26 assigned to saffron	24 assigned to saffron

Discussion:-

Alzheimer's disease extensive public health problem. AD is a disease that is progressively being diagnosed around the world.it is one of the significant, difficult and troublesome conditions not for the patient even or their families. Development of AD progressively new symptoms is common in AD patients. The source of the on set of AD is manifold and even genetic predisposition, older age and environmental predisposition [1].

Currently, there is no reliable pharmacological treatment for patients with AD. Many natural compounds and their selective molecular targets seems to decrease the onset of AD, late the progression of disease, and allow for regaining targeting more pathological causes through anticholinergic, antioxidant and anti-inflammatory effects and less adverse events. New agents also failed in modifying disease in clinical trials pushing the field to re-considering its underlying mechanism about disease pathophysiology, [2]

Because of this current AD therapy is a challenge for modern medicine due to the insufficient theories of the disease pathogenesis and the ineffectively of drugs to stop the progression of mild AD.[3]

The current study indicates that the saffron capsules are useful for the treatmentof patients with mild to moderate AD as proved by improvement in the CDR-SBscale. Relatively so many studies are emerging on the same topic to prove thatsaffronhasefficacyinthetreatmentofAD. However, the reare increased evidences to sugges the possible efficacy of saffron capsules in the management of AD (Papandreou et al. 2006: Akhondzadeh et al. 2009)

These studies proved that or alsaffron improved the dementia of mice predamaged with thanoland saffron prevents the inhibitory effects of ethinalon LT Pinmice. (Sugiura et al.1995, Papandreou et al.2006, pitiskas N et al 2006, pitiskas Nand Zissopoulos S et al 2007). Minimal doses of saffron inhibit the extinction ofrecognition memory in the object recognition test and reverse the scopolamine –induced performance in the passive avoids a cetask (Sugiuraetal.1995). In line with previous studies

Alavizadeh, S. H **et al. (2019)**, our findings recommend that saffron may help decrease Aβ aggregation and increases its clearance, less or no the toxic effects of amyloid plaques in the brain." Likely to Majeed, M., & Gupta, S.**. (2019)**, our study found that administration saffron significantly increased cognitive performance in AD patients, selectively in **memory recall** and **executive function**, recommending it could be a valuable add on therapy to traditional AD medications." Similar like previous studies Jafari, M., &Nourbakhsh, M. (2017) ,Majeed, M., & Gupta, S. (2019). The additional major advantages of saffron as a treatment for Alzheimer's is its **wide safety profile**. Not like conventional AD drugs, saffron causes less or no side effects, making it a favorable option for patients who cannot tolerate pharmaceutical treatments."

The results of this trial are consistent with the result of those basic studies (Sugiuraetal .1995, Papandreou et al. 2006, pitiskasN et al 2006, pitiskasN and ZissopoulosS et al 2007)as well as the reported antioxidant and anti amyloido genicactivity of an saffron stigmas. (PapandreousM A et al2006).

The limitations of present study include the small number of patients and arelatively short period of followup. Therefore, further controlled studies should be under taken. The use of her balme dicines in the treatment of AD should be compared with the pharmacological treatment currently inuse.

Conclusion:-
This study indicates that at least in the short-term saffron capsule is safe andeffective in mild – moderate AD. More randomized controlled studies are required further verify this her balremedy.
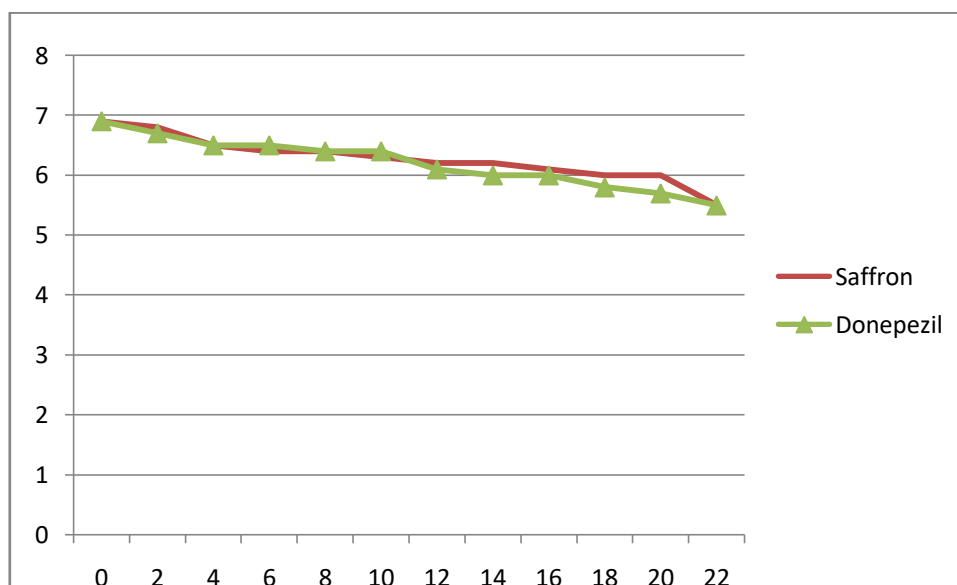

Fig. 1:- mean±SDscoresofthetwoprotocolsontheCDR-SB score,nsnosignificant.

Table 1:-

	Saffrongroup	Control group	P
Gender	Male:15,female:12	Male:15,female:12	nsnsn
Age(mean±SD)Levelofeducation	73.55±4.98(year)	74.15±5.08(year)	s
	Underdiploma:15Diploma:7	Underdiploma:17Diploma:6	
Timesincediagnosis(mean±SD)	Higherdiploma:519.65±9.19(month)	Higherdiploma:418.05±4.10(month)	ns

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