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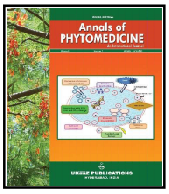

Review article: Open access

Systematic study on protective role of date palm (*Phoenix dactylifera* L.) on central nervous system disorders

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Abstract

Present study was designed to screen the role of *Phoenix dactylifera* L. (*P. dactylifera*) in CNS disorders. All the records were summarized according to PRISMA statement of systematic reviews. By applying identification, exclusion, eligibility and inclusion criterias, 17 original research articles were selected. In these studies, *P. dactylifera* was used as either long term dietary supplementation or aqueous or ethanolic or methanolic extracts. These studies reported different activities such as anti-Alzheimer's, anticonvulsant, cerebral anti-ischemic, neuroprotective, anxiolytic, nootropic and antipsychotic. Mechanisms underlying anti-Alzheimer's activity of *P. dactylifera* were antioxidant, anxiolytic, cholinomimetic and anti-inflammatory actions. Anticonvulsant activity was due to GABA facilitatory action and blocking of NMDA action. Antioxidant nature of flavonoids, tannins and phenols of *P. dactylifera* showed neuroprotective and cerebral anti-ischemic actions. whereas antipsychotic actions were due to decreased serotonergic and dopaminergic transmissions and increased cholinergic transmission. This systematic study successfully establishes and supports protective role of *P. dactylifera* in treatment of CNS related disorders and put forth the path to carry out the meta-analyses for increasing the use of safer plant based remedies.

1. Introduction

Phoenix dactylifera L. belongs to Arecaceae family and commonly called as date palm. It is a foremost cultivated crop since last 5000 years in the Middle East, Arabian and North African countries (Baliga *et al*., 2011). Chief phytoconstituents found in fruits are anthocyanins such as pelargonin; phenolics such as caffeic acid, chlorogenic acid, cinnamic acid, coumaroylquinic acid, ferulic acid, gallic acid, hydrocaffeic acid o-coumaric acid, p-coumaric acid, p-hydroxybenzoic acid, protocatechuic acid, sinapic acid, syringic acid, vanillic acid, xanthoxylin acid and 5-o-caffeoyl shikimic acid (Karasawa *et al*., 2011); phytoestrogens such as coumestrol, daidzein, formononetin, genistein, glycitein, lariciresinol, matairesinol, pinoresinol and secoisolariciresinol (Thompson *et al*., 2006); carotenoids such as β-carotene, lutein, antheraxanthin, violaxanthin and neoxanthin (Al-Rimawi and Odeh, 2015). Flavonoids include isoquercetrin, rutin (Hamad *et al*., 2015), diglycosidic apigenin, mono, di and triglycosidic form of both luteolin and Quercetin (Hong *et al*., 2006), Diosmetin 1 (diosmetin 7-O-β-L-arabinofuranosy (1'!2)-β-D-apiofuranoside) and Diosmetin 2 (diosmetin 7-Oβ-D-apiofuranoside) (Michael *et al*., 2013).

Traditionally, it was commonly used for varied conditions in different parts of the world. In Morocco, people used it for diabetes and hypertension (Vickers, 2017); pulp boiled in milk as tonic and powdered mixture of almonds, dates, pistachio nuts, spices, quince seeds and sugars as nourishing diet for pregnant and lactating mothers (Puri *et al*., 2000); and also used for anti-aging activity (Meer *et al*., 2017), bronchitis, burning sensation, cough, gastropathy, nephropathy, rheumatism and sexual debility (El-Hilaly *et al*., 2018).

Within a short span of last 50 years (1969 to 2019) marvellous beneficial uses of the date fruit have been validated scientifically with *in vitro* and *in vivo* studies. Yeh *et al*. (2009) showed the expression of antioxidant enzyme genes in animals treated with date's p-coumaric acid, Chaira *et al*. (2009) showed antiradical activity of date flavonoids. Phenolic acids were reported with antimutagenic activity (Birosova *et al*., 2005). Abuharfeil *et al*. (1999) reported antihaemolytic effect of date steroids. Tapas *et al*. (2008) reported membrane stabilizing effect of date constituents like anthocyanins, carotenoids, flavonoids and procyanidins, Orhan (2010) reported antifungal activity of date ûavonoids, Jassim and Naji (2010) reported antiviral activity of date fruits. Antihyperlipidemic and cardioprotective activity were reported with anthocyanins (Finne Nielsen *et al*., 2005). Hepatoprotective activity was reported with apigenin (Zheng *et al*., 2005) caffeic acid and quercetin (Janbaz *et al*., 2004). Nephroprotective activity was reported with quercetin (Abdel-Raheem *et al*., 2009). Anticancer activity was reported with β-glucan (Fullerton *et al*., 2000). Isorhamnetin, kaempherol and quercetin were reported with immunostimulatory activity (Akbay *et al*., 2003). Genistein was reported with gonadotropic activity (Eustache *et al*., 2009). The antidiabetic activity was reported with diosmetin 1 and 2 (Al-Harrasi *et al*., 2014), genistein and daidzein (Choi *et al*., 2008). β-sitosterol (Field *et al*., 1997) and stigmasterol (Batta *et al*., 2006) were reported with hypocholesterolemic effect. Antidiarrheal activity was reported with aqueous extract of date fruits (Kumar *et al*., 2010). By keeping in consideration, the vast clinical applications of *P. dactylifera*, current study was designed to carry out the systematic review of animal research data available in the reported literature.

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2. Materials and Methods

2.1 Study design

Different databases such as Pubmed, Science Direct, Scopus, Springer and Google Scholar were used to carry out the in-depth search of literature. Mesh terms which were used for carrying out systematic survey are: three plant related terms *viz*., "*Phoenix*" OR "*Phoenix dactylifera*" OR "Date Palm" were used individually in combination with each of the CNS disorder related term *viz*., "ADHD" OR "Alzheimer's" OR "Anxiety" OR "Anxious" OR "Attention Deficit" OR "Attention Deficit Disorder" OR "Attention Deficit Hyperactivity Disorder" OR "Autistic Spectrum Disorder" OR "Autism" OR "Brain" OR "Central Nervous System" OR "CNS" OR "Cognitive Impairment" OR "Delusion" OR "Dementia" OR "Depression" OR "Depressive Symptoms" OR "Generalized Anxiety Disorder" OR "Hyperactivity Disorder" OR "Major Depression" OR "Neurodegenerative Disease" OR "Neurological Disorders" OR "Neuropsychiatric Disorder" OR "Psychological Disorder" OR "Psychosis" OR "Psychotic Disorder" OR "Schizophrenia" OR "Trauma".

2.2 Identification, exclusion, eligibility and inclusion basis

All the published original research studies which used any of the above plant related terms in combination with CNS disorders related terms were identified. Records which have been excluded were duplicate articles and articles which were not relevant to the aim of work. Further screenings of records were conducted to remove items which were not eligible for systematic study. Records which were not eligible were abstracts, commentaries, protocols, book chapters and papers published in conferences, congress, meetings, scientific sessions and symposiums because of inadequate information. Finally, full text articles which were relevant to the aim of work were selected for the study.

3. Results

3.1 Search results

Intensive screening of all databases identified 4014 records. Extracted data was summarized by using PRISMA guidelines (Figure 1). 1717 duplicate records were excluded; from remaining 2297 records 1754 were excluded as they were not relevant to the aim of the work. 543 records were further screened and 526 records were found not eligible and were removed and finally, 17 full text articles were retained for the systematic study. The summary of these articles is presented in Table 1. Moreover, the mechanism of *P. dactylifera* was explained in Figure 2.

3.2 Anti-Alzheimer's activity

Among the included studies, five were reported with anti-Alzheimer's activity in which three studies used date palm as a part of the diet and among the other two; one used aqueous date fruit extract (ADFE) and another used date seed extract (DSE). Subash *et al*. (2015) evaluated the effect of date palm fruit in the diet on the transgenic mouse model of Alzheimer's disease (AD) (APPsw/Tg2576). 2% and 4% date supplementation for 14 months in APPsw/Tg2576 mice restored locomotor activity, *i.e.*, muscular coordination (rotarod and open field tests), improved escape latency (morris water maze test), reduced anxiety levels (elevated plus maze test), improved position discrimination learning ability (T-maze test). There was also a significant reduction in circulating levels of human amyloid β (Aβ) 1-40 and Aβ1-42 in APPsw/Tg2576 mice received date rich diet. With another group of scientists, Subash *et al*. (2015) screened the effects of 2% and 4% dates supplementation for 15 months on oxidative stress and antioxidant status by using APPsw/Tg2576 mice. Dietary supplementation considerably reduced the lipid peroxidase (LPO) and protein carbonyl content (PCO) levels, restored normal levels of antioxidant enzymes, alternated the AchE activity and improved Na^+-K^+-ATPase activity. Later on, Essa *et al.* (2015) reported protective effects of only 4% date palm dietary supplementation against the neuroinflammation in APPsw/Tg2576 mice. The study resulted in recovery of ATP levels (45%) and significant decrease in plasma cytokines (*viz*., IL-2, IL-3, IL-4, IL-5, IL-9, IL-10 and Eotaxin), cortex and hippocampus region neuropeptides (*viz*., Aβ1-40, Aβ1-42, IL-1β, TNF-α, and IL-6) on supplementation with date palm. This study also covered beneficial effects of pomegranates and figs along with date palm.

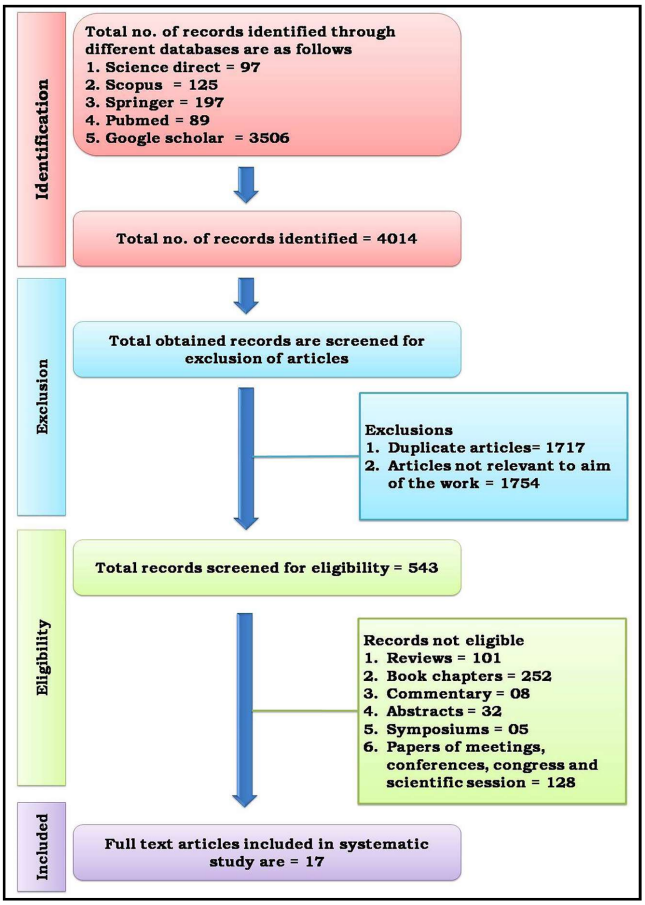

Figure 1: Flow chart explaining identification, exclusion, eligibility and Inclusion process by using PRISMA guidelines.

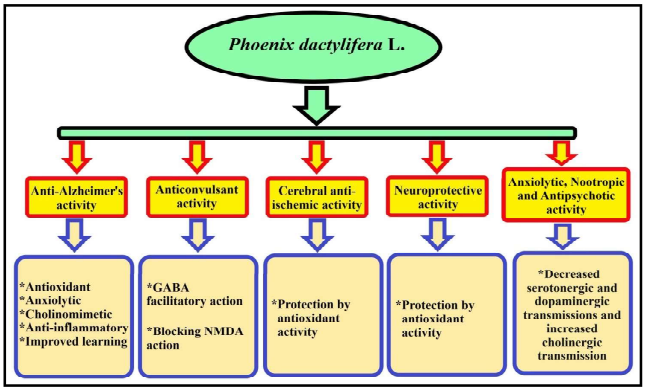

Figure 2: Mechanism of action of *P. dactylifera* in different CNS related disorders.

Table 1: Brief summary of studies related to *P. dactylifera* and CNS disorders

S.No.	Diet / Extract / Constituent (Dose-mg/kg)	Part used	CNS related activity	Method of induction	Study sample	Duration of study	Parameters	Results
1.	Diet (2% and 4%)	Fruit	Anti-Alzheimer's activity	APPsw/Tg2576 Transgenic mice	24	14 months	Spatial memory and learning ability, psychomotor coordination, anxiety and levels of Plasma amyloid beta (1-40 & 1-42)	2% and 4% date diet supplementation showed beneficial effects on cognition, locomotor activity and significantly lowered both plasma amyloid beta proteins (Subash *et al*., 2015).
2.	Diet (2% and 4%)	Fruit	Anti-Alzheimer's activity	APPsw/Tg2576 Transgenic mice	24	15 months	Oxidative damage, levels of antioxidant and membrane bound enzymes	2% and 4% date diet supplementation reduced oxidative stress, increased antioxidant enzyme levels and restored membrane bound enzyme activities (Subash *et al*., 2015).
3.	Diet (4%)	Fruit	Anti-Alzheimer's activity	APPsw/Tg2576 Transgenic mice	80	15 months	Inflammatory cytokines estimation, brain content of Amyloid β (1-40 & 1-42), estimation of ATP, assessment of IL-1β, TNF-α and IL-6	4% date diet supplementation provides protection against the inflammation in APPsw/Tg2576 Transgenic mice brain (Essa *et al*., 2015).
4.	Aqueous extract (100, 200 & 400)	Fruit	Anti-Alzheimer's activity	Scopolamine (0.4mg/kg) & STZ (0.4mg/kg) induced memory loss	126	30 days	Antioxidant activity, Nootropic activity, AChE activity	ADFE showed antioxidant, nootropic activity and averted the chemical induced memory deficiency in mice (Hussain *et al*., 2015).
5.	Methanolic extract (80)	Seed	Anti-Alzheimer's activity	Beta-amyloid induced hippocampal damage	24	13 days	Learning and memory evaluation, Caspase-3 expression and neuronal degeneration.	DSE protected CA1 area of hippocampus, improved learning and memory, decreased caspase-3 expression (Dehghanian *et al*., 2017).
6.	3,4-dimethoxy toluene (100)	Spathe	Anticonvulsant activity	MES, PTZ, Pic and Nic induced convulsions	48	1 day	Convulsions and mortality	DMT showed anti Convulsant action and also showed protection against mortality (Al-Taher, 2008)
7.	Methanol-water (4:1 v/v) (30, 100 & 300)	Fruit	Cerebral anti-ischemic activity	BCCAO (micro aneurysmal clips for 30 minutes, followed by 45 min reperfusion)	30	15 days	Biochemical Analysis, Histopathological examination	MDFE showed significant neuroprotection by reversing the changes in biochemical parameters of brain and also preventing histopathological alterations (Pujari *et al*., 2011).
8.	Methanolic extract (30, 100 & 300)	Fruit	Cerebral anti-ischemic activity	BCCAO (long term hypo perfusion for 15 days)	30	15 days	Biochemical analysis-estimation of TP, SOD, LPO, CAT, GSH, GPx, GST, GR. Histopathological studies	MDFE provided significant neuroprotection by reversing the alterations in the biochemical parameters of the brain produced due to the oxidative stress induced by BCCAO. Pretreatment also reserved histoarchitecture of CA1 Hippocampal region (Pujari *et al*., 2013).
9.	Methanolic extract (30, 100 & 300)	Fruit	Cerebral anti-ischemic activity	BCCAO (Micro aneurysmal clips for 5min followed by reperfusion for 4 days.)	30	15 days	Behavioral testing-open field test, morris water maze; biochemical analysis-estimation of TP, SOD, LPO, CAT, GSH, GPx, GST, GR; histopathological examination.	MDFE exhibited significant neuroprotection against oxidative stress, neuronal damage and spatial learning and memory impairment induced by permanent BCCAO (Pujari *et al*., 2014).
10.	Aqueous extract (80)	Seed	Cerebral anti-ischemic activity	MCAO (occlusion for 30 min, followed by reperfusion for 48 hours)	29	3 days	SOD, MDA, TAS measured, Morphological studies and behavioral activity	DSE showed decrease in neuronal damage, improved muscle coordination, decreased MDA, increased SOD and TAS as compared to control group (Kalantaripour *et al*., 2012).
11.	Aqueous extract (350)	Fruit	Neuroprotective activity	Lead acetate (800 mg/kg) induced neuronal damage in the occipital cortex	15	8 days	Histological examination.	ADFE conferred neuroprotective role against lead acetate induced degeneration of neuronal cells (Joseph *et al*., 2014).
12.	Aqueous extract (1000 & 1500)	Fruit	Neuroprotective activity	Lead acetate (120 mg/kg) induced cerebellar damage	24	28 days	Histological examination of the cerebellar cortex with H and E stain	ADFE ameliorated lead acetate induced cerebellar damages such as perineuronal vacuolations and cytoplasmic shrinkage in purkinje cells of cerebellar cortex (Yusuf *et al*., 2017).

S.No.	Diet / Extract / Constituent (Dose-mg/kg)	Part used	CNS related activity	Method of induction	Study sample	Duration of study	Parameters	Results
13.	Ethanol extract (500 & 1000)	Fruit	Neuroprotective activity	Lead-acetate (120 mg/kg) induced cortical cerebral alterations	20	35 days	Histological and histochemical examination	EDFE ameliorated degenerative changes in cerebral cortex (Lazarus *et al*., 2018).
14.	Aqueous extract (500, 1000 & 1500)	Fruit	Neuroprotective activity	Artesunate (300 mg/kg) induced cerebellar damage	20	7 days	Histopathological and histochemical examination.	ADFE showed neuroprotective effect by inhibiting the formation of vacuoles, degeneration of purkinje fibers and histoarchitectural change of cerebellum (Agbon *et al*., 2014).
15.	Aqueous and ethanol extract (Both 500, 1000 & 1500)	Fruit	Neuroprotective activity	Artesunate-Amodiaquine induced Cerebellar cortex damage	36	28 days	Necrosis, Chromatolysis and vacuolations of cerebellar cortex	Both extracts preserved histoarchitecture in dose dependent manner (Budaye *et al*., 2018)
16.	Ethanol extract (250 & 500)	Fruit	Neuroprotective activity	Pentobarbitone induced sleeping time, open field test and hole board test.	24	2 days	Sleeping time, locomotor activity and exploratory behavior	Extended sleeping time and reduced locomotor activity and exploratory behavior (Sheikh *et al*., 2016).
17.	Methanolic extract (30, 100 & 300)	Fruit	Anxiolytic, Nootropic and Antipsychotic activities	Hot-plate test, haloperidol induced catalepsy, sodium nitrate induced respiratory arrest, MES induced convulsions	228	7 days	Motor coordination, locomotor activity, analgesic, anxiolytic and anticonvulsant effects, cognition and hypoxic effects.	MDFE possesses significant anxiolytic, analgesic, nootropic and antipsychotic activities (Vyawahare *et al*., 2009).

Instead of using long term date dietary supplementation, Hussain *et al*. (2015) used ADFE for screening anti-Alzheimer's activity. ADFE showed no AChE activity, a dose-dependent DPPH free radical scavenging activity (IC50=3.5mg/ml) and significant increase (p<0.05) in Inflexion ratio in elevated plus maze test. Further, ADFE also showed statistically significant p<0.001 and p<0.01 increase in Inflexion ratio in scopolamine and Streptozotocin (STZ) induced amnesia respectively on elevated plus maze apparatus. Later on Dehghanian *et al*. (2017) evaluated the neuroprotective effect of DSE in the treatment of AD in the rat model. DSE showed free radical scavenging activity against DPPH radicals, significant decrease in path length and escape latency in Morris water maze test, decrease in expression of caspase-3 and detrimental effects of β-amyloid induced insults.

3.3 Anticonvulsant activity

Only one study was reported with anticonvulsant efficacy of date palm. 3, 4-dimethoxy toluene (DMT), the major constituent of date palm spathe was reported to delay both the onset of convulsions and onset of death and produced 50-100% protection against mortality in pentylenetetrazole (PTZ), picrotoxin (Pic), nicotine (Nic) and maximal electroshock (MES) epileptic models (Al-Taher, 2008). Moreover Vyawahare *et al*. (2009) reported no significant action of methanolic date fruit extract (MDFE) in MES induced convulsions.

3.4 Cerebral anti-ischemic activity

Cerebral ischemia is also a major cause of neuro degeneration. A total of four studies were identified in which date palm showed protective role in cerebral ischemic conditions. Among them three were conducted on rats challenged with global cerebral ischemia and one on rats challenged with focal cerebral ischemia. Pujari *et al*. (2011) conducted a study to evaluate the antioxidant and neuroprotective effects of MDFE against global cerebral ischemia induced by bilateral common carotid artery occlusion (BCCAO) in rats. The 15 days pre-treatment with MDFE significantly attenuated neuronal loss and also attenuated all biochemical parameters except depletion of glutathione peroxidase (GPx) and glutathione S-transferase (GST) levels. Later on Pujari *et al*. (2013) reported neuroprotective effect of MDFE against BCCAO challenged rats. MDFE decreased neurological scores (MCgraw, 1997), attenuated the change of all biochemical enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), GST, GPx, glutathione reductase (GR), malondialdehyde (MDA) and also blocked necrotic changes of Cornu Ammonis (CA) as compared to BCCAO control rats. Similarly Pujari *et al*. (2014) reconfirmed the neuroprotective role of MDFE against BCCAO challenged rats. Post treatment for 15 days with MDFE showed a significant decrease in MDA, significant increase in GSH, GPx, GST, CAT, SOD, improved memory and spatial learning (Morris water maze test), decreased anxiety and restlessness (open field test); and attenuated shrinkage and necrosis of neurons (histopathological examinations).

Kalantaripour *et al*. (2012) showed a protective role of DSE against focal cerebral ischemia induced by Middle Cerebral Artery Occlusion (MCAO). In the experimental group after reperfusion 80mg/kg of DSE was administered by the intraperitoneal route. These animals showed 30.33% of neuronal damage, attenuation of neural degenerative changes, improved motor coordination, a significant decrease in MDA and increase in SOD, total antioxidant levels (TAS) as compared to the ischemic group.

3.5 Neuroprotective activity

A total of six studies were reported with neuroprotective activity of date fruit extract. In first three studies lead acetate was used, in fourth study alone artesunate was used and in fifth study artesunate and amodiaquine was used in combination to induce cerebellar damages. Joseph *et al*. (2014) and Yusuf *et al*. (2017) reported normal cytoarchitecture in cortical regions of lead acetate challenged animals after treatment with ADFE. These two studies also reported the normal histological cerebral cortex appearance in animals receiving only ADFE without lead acetate challenge. Later on Lazarus *et al*. (2018) reported mild histo-architectural distortions such as pyknosis and cytoplasmic vacuolation in lead acetate challenges animals treated with ethanol date fruit extract (EDFE).

Agbon *et al*. (2014) reported the animal groups treated with ADFE challenged with artesunate showed mild distortion of histoarchitecture of the cerebellar cortex. Later on Budaye *et al.* (2018) reported more improved effects of ADFE than EDFE in cytoarchitecture of cerebellar cortex of Artesunate and Amodiaquine challenged rats.

Animals treated with EDFE of all three varieties, *viz*., Ajwah, Safawy and Sukkari showed increased duration of sleep and reduced time for the onset of sleep (Pentobarbitone induced sleeping time test), decreased locomotor activity (Open field test), decreased number of head dippings (Hole board test), decreased writhing (Acetic acid test), increased response time (Hot plate test) as compared to control mice. HPLC analysis showed the presence of transferulic acid in all the 3 varieties; (+) catechin and (-) epicatechin in Ajwah and Safaway; caffeic acid and P-coumaric acid in Sukkari only and Rosmarinic acid in Ajwah only (Sheikh *et al*., 2016).

3.6 Anxiolytic, nootropic and antipsychotic activities

Animals treated with MDFE showed proper muscular coordination, optimum locomotor activity (Actophotometer test), significant increase in reaction time (Hot plate test), anxiolytic activity (Elevated plus maze test and double unit mirrored chamber test), intensified catalepsy (Haloperidol test), significant delayed in the onset of death (Sodium nitrite test) and significant increase in discrimination index (Object recognition test) as compared to control animals (Vyawahare *et al*., 2009).

4. Discussion

Anti-Alzheimer's activity of date palm was screened by using APPsw/Tg2576 mice. Abnormal behavior of this mouse was due to the anxiogenic effect caused by the deposition of β-amyloid peptides. Formation of β-amyloid plaques was also accelerated by IL-1β, IL-6 and tumor necrosis factor-α (TNF-α) (Patterson, 1995). β-amyloid plaques and neurofibrillary tangles activate astrocytes and microglia (Engelhart *et al*., 2004). These animals showed increased levels of different inflammatory cytokines, LPO, PCO levels and AChE activity and inhibition in Na^+-K^+-ATPase activity, decreased circulating levels of Aβ1-40 and Aβ1-42, significant decreased levels of ATP (a requisite for neuronal survival) and oxidative parameters in cerebral cortex and hippocampus regions. Since, drug treatment is not curative but it is supportive and will not alleviate the exact root cause of the disease (Kuo and Rajesh, 2017). Many studies have reported the use of fruits and vegetables in the diet as a treatment option for AD. Subash *et al*. (2015) and Essa *et al*. (2015) reported that date palm dietary supplementation for 14 to 15 months restored all these abnormalities of APPsw/Tg2576 mice. These beneficial effects of date fruits were due to anxiolytic activity. The reduction of inflammatory cytokines in both plasma and brain were due to the antioxidant action of phytoconstituents like ferulic acid (Kim *et al*., 2004), protocatechuic acid (Matsumoto *et al*., 2004) and caffeic acid (Huang *et al*., 2013) against Aβ induced toxicities. Al-Shahib and Marshall, (2003) also reported the existence of polyphenols in date palm fruits thus proving their role to neutralize the toxicity of oxygen free radicals

In some studies, instead of using APPsw/Tg2576 mice, normal mouse was used to develop AD. Scopolamine and STZ was used to induce amnesia which was due to oxidative stress. This was relieved by ADFE indicating its cholinomimetic potential. Further, the role of AChE was screened and no ADFE dose produced a significant decrease in AChE activity revealing more support towards cholinomimetic activity. Different phytoconstituents of ADFE like phenols and flavonoids plays a major role in relieving oxidative stress (Hussain *et al*., 2015). In another study β-amyloid was injected to develop AD. β-amyloid plaques causes damage to the cell membrane and severe degenerative changes in cortical neurons. These detrimental effects were due to increased expression of caspase-3 and generation of reactive oxygen species. All these β-amyloid induced insults are prevented by antioxidant property of DSE (Dehghanian *et al*., 2017). Vayalil, (2012) also reported the antioxidant, neuroprotective potential of DSE. Thus usage of fruits is beneficial in controlling AD. Many other fruit extracts were also reported with anti-Alzheimer's activity *viz.*, β-amyloid toxicity was controlled by walnut extract (Muthaiyah *et al*., 2011), memory improvement by pomegranate (Hartman, 2006), cognitive improvement by *Ginkgo biloba* (Oken *et al*., 1998).

After AD another challenging CNS related disorder is epilepsy. According to the 20th June 2019 report of WHO, 50 million people globally, are suffering from epilepsy- a chronic brain disorder. Globally, research was focused on discovering new potent synthetic molecules like coumarin derivatives (Tippu *et al*., 2018) and plant phytoconstituents (Imad Uddin *et al*., 2017) for the treatment of epilepsy. Efficacy of DMT against PTZ and Pic induced seizures was found to be due to stimulation of GABA pathway and an increase in GABA levels respectively. Moreover, protection against Nic-induced seizures was due to blocking of NMDA receptor or by decreasing NO formation.

Cerebral ischemia is also a major cause of neuro degeneration. BCCAO caused decrease in levels of CAT, GSH, GST, SOD, GR, GPx, and significant increase in the levels of LPO, neurological score, infiltration of inflammatory mediators, vacuolization and death of neurons in the CA, shrinkage and atrophy of neurons in other brain areas of the ischemic rats as compared to the sham group rats. These animals also showed anxiety and restlessness, decrease in memory and spatial learning. Whereas animals with focal ischemia showed death of cortical neurons (indicated by swelling of neuronal organelles, aggregation of chromatin and dark nucleus), motor incoordination, weak muscles, a significant increase in MDA and decrease in SOD and total antioxidant levels. These damaging effects of BCCAO and MCAO were relieved with polyphenolic compounds (flavonoids) of MDFE and DSE. Hence these findings provide a promising use of *P. dactylifera* in stroke and vascular dementia in AD and age-related memory disturbances. (Pujari *et al*., 2014; Kalantaripour *et al*., 2012).

Lead acetate is toxic to both humans and animals (Wade *et al*., 2002). Animals challenged with lead acetate showed neurodegenerative effects like shrinkage of cytoplasm, satellitosis, perineuronal vacuolation in molecular layer cells and Purkinje cells of the cerebellar cortex. All these lead acetate insults are controlled in animals treated with ADFE and EDFE. The protective role of *P. dactylifera* was due to antioxidant, chelating and scavenging activity of flavonoids (Lazarus *et al*., 2018). Widely used antimalarial drug artesunate either alone or in combination with Amodiaquine was also reported to cause distortion in the histoarchitecture of the cerebellar cortex such as neuronal cell loss, neuronal vacuolation, complete loss of Purkinje cell dendrites, and nuclear pyknosis. Neuroprotective role of ADFE against these insults was may be due to the presence of antioxidant compounds like flavonoids, saponins, and tannins (Agbon *et al*., 2014; Budaye *et al.,* 2018). These studies are in accordance with Pasha *et al*. (2015) where these constituents were reported to possess potent antioxidant activity.

Moreover, *P. dactylifera* was also reported to possess analgesic, anxiolytic, nootropic and antipsychotic activities. These may be due to decreased serotonergic and dopaminergic transmissions and increased cholinergic transmission (Vyawahare *et al*., 2009). Later on Sheikh *et al*. (2016) reported analgesic and neuropharmacological activity of three varieties of dates, *viz*., ajwa, safawy and sukkari. The effect of ajwa extract was stronger than the safawy and sukkari extracts due to the highest concentration of transferulic acid.

5. Conclusion

This study summarizes many beneficial aspects of the miracle plant date palm. Authors can put forth the vast usage of this plant all over the world for long times not only as a medicine but also as a part of the diet. This review covered three studies showing the Neuro-beneficial effects of diet supplementation of date fruits. The study also recapitulates various underlying mechanisms of *P. dactylifera, viz*., antioxidant, anxiolytic, cholinomimetic, anti-inflammatory, GABA facilitator and blocking NMDA action. All these mechanisms may be due to the vast variety of phytoconstituents present in seeds and fruits of this plant. *P. dactylifera* possesses neurobehavioral and neuroprotective properties because of these essential mechanisms and possesses treatment efficacy in many CNS related disorders like epilepsy, Alzheimer's disease, cerebral ischemic conditions, anxiety and psychosis. *P. dactylifera* due to its antioxidant action also provided protection against amodiaquine, artesunate and lead acetate induced cerebellar damages. By taking into consideration of all the above-discussed postulates, this study promotes to carry out a meta-analysis along with its wider and safer usage. Leading molecules should be isolated and developed from *P. dactylifera* which may serve as a recognizable treatment option for these globally challenging diseases.

Conflict of interest

The authors declare that there are no conflicts of interest in the course of conducting the research. All the authors had final decision regarding the manuscript and decision to submit the findings for publication.

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