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Review Article
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A Systematic Review of Preclinical and Clinical Studies on Therapeutic Potential of *Piper nigrum* on Cognitive Impairment in Alzheimer's Disease and other Biological Conditions of Memory Loss

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Abstract:
Piper nigrum is one of the most familiar spices due to its' pharmacological and physiological properties. Piperine is a main active alkaloid of *Piper nigrum* with a broad spectrum of biological activities including anti-aging, anti-inflammatory, anti-cancer, anti-depressant, and cognition enhancer, thus it is effective in correlated diseases. Principally, the useful effects of piperine in neurological conditions have been confirmed in in-vitro and in-vivo studies. Beta-caryophyllene a major constituent of its essential oils well known for neuroprotective and specially nootropic effects. Some clinical trials have reported that *Piper nigrum* possesses preventive and therapeutic effects in memory loss related disorders.
The current systematic review aimed to consider the effects of *Piper nigrum* on cognition and memory performance as well as Alzheimer's disease. Electronic databases including Scopus, PubMed, Web of Science, ProQuest, and Embase were searched with the keywords "piper nigrum" OR piperine OR "black pepper" OR β-caryophyllene OR beta-caryophyllene AND "Alzheimer's disease" OR dementia OR amnesia OR memory OR cognitive OR cognition OR nootropic until 18 January 2020. Only in-vivo and clinical studies with sufficient data were included in this review.
The results of this systematic review showed that *Piper nigrum* may have significant effects on memory and cognitive performance assessed by related tests though more randomized clinical trials are needed to validate its' indication in cognitive impairments.
Systematic review registration number: 22309

Keywords: *Piper nigrum*; piperine; beta-caryophyllene; Alzheimer's disease; Dementia; Cognition

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1. Introduction

In acknowledgment of each 12 studies on cancer, there is only 1 study on all types of neurodegenerative disorders; it demonstrates the aspects of the research gap in this field of study. The most common neurodegenerative disease is Alzheimer's disease (AD), which records for 60–70% of cases with dementia. Approximately 80 % of people in the world concerns for an increasing rate of dementia [1]. According to World Health Organization's (WHO) reports in 2013, 35.6 million people worldwide suffer from this disease and as the lifespan of the aged people grows, it is expected that the incidence will be doubled by 2030 and triplicated by 2050 [2]. Aging is a normal process that shows its face with various ailments and chronic disabilities. Neurodegeneration is a primary happening occurrence of aging with reflecting dysfunctions such as dementia [3]. Regardless of the wide spectrum of researches to improve cure, currently, there aren't effective routes of treatment for the declining incidence of cognition disorders [4]. Clinical symptoms of AD are consisting of a reduction in cognitive tasks, dealings in ordinary per diem responsibilities, and conversion in behavioral actions. Within these complaints consequence AD, memory dysfunctions are the main problem in patients. Various reasons take part in the pathophysiology of AD. The formation of plaques from peptides of amyloid- β (Aβ) is a feature of starting AD. Phosphorylation of tau protein precipitated as intracellular neurofibrillary tangles (NFTs) according to the increase

in the activity of protein kinase enzymes or reduction of activity in phosphatase enzyme is another pathophysiological representative of AD [5]. Genes and Apolipoprotein E (APOE) correlation and specially APOE ε4, increase the possibility of the affliction of AD with commencing, facilitate and accumulation of segmentation of peptides of Aβ. In brain tissue of AD suffering subjects and healthy oldsters, mitochondrial activity dysfunctions can lead to the release of oxidative free radicals and oxidative damages which in them reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a role [6]. Accumulation of Aβ peptides in the brain activates astrocytes and microglia and causes in the release of biochemical and induced inflammation in AD patients [4]. Also, enzymes required for forming acetylcholine (Ach) neurotransmitter decline in AD. Another mechanism can also interact in memory and learning procedures such as N-methyl-D-aspartate receptor (NMDA) reduction. Furthermore, environmental factors are important reasons in AD as a neurodegenerative disease [5].

However the available drugs' efficacy is also uncertain, selective therapies for AD are based on inhibition of cholinesterase and NMDA antagonist mechanisms, which are also symptomatic. Alternating phytopharmaceuticals into an anti-AD drug is one of the treating routes of AD. Today Tacrin, Rivastigmine, Physostigmine, Donepezil, Memantine, and Galanthamine are available in the market [7]. These drugs have side effects like anorexia, nausea, diarrhea, vomiting, insomnia, etc. or have a short half-life, variable bioavailability which leads to narrow therapeutic indications [8]. There is a growing demand for the usage of natural products for the control and management of different diseases such as AD [9, 10]. Black pepper (*Piper nigrum* L.) from the family of Piperaceae is one of the most usable spices in the world and because of pungent constituent named piperine (PIP) is well known. Piperine is a main active alkaloid of *piper nigrum* (PN) which many applications such as anti-inflammatory effects, anti-nociceptive, anti-seizure, anti-cancer, bioavailability enhancer anti-depressant and cognitive ability enhancer are stated for it [11]. Structure-Activity Relationship for piperine depends on the existence of the polyene bond system which makes it a potent antioxidant, also the existence of nitrogen tertiary for example in Ach can lead to inhibition of acetylcholinesterase (AchE) enzyme [12, 13]. Beta-caryophyllene (BCP) was known as a natural selective agonist of cannabinoid receptor 2 (CB2), it is the major constituent of the essential oil of *Piper nigrum* and is also available in many other medicinal plants such as *Origanum vulgare*, *Cinnamomum* spp., *Syzygium aromaticum*, *Rosmarinus officinalis*, and *Thymus serpyllum*. This natural bicyclic sesquiterpene possesses an extensive assortment of pharmacological effects containing anti-nociceptive, anti-microbial, antifungal, neuroprotective, antioxidant and anti-inflammatory activity [14]. BCP special features make it a great choice to be studied in neurological conditions; especially AD, these manifesting characteristics stated as; approved by FDA, its' high safety therapeutic index, its suitable lipophilicity to cross the blood-brain barrier and reaching the brain, and its' imaginary effect on locomotor activity [15].

The lack of effective therapeutic agents combat AD, it has led scientists to look for alternative approaches in order to treat or prevent AD. Accumulating evidence suggests neuroinflammation, oxidative stress, mitochondrial dysfunction or autophagy as potential etiologies for AD. It is also documented that IL-6, TNF-α, and IL-1 which were pro-inflammatory cytokines was intensely mitigated by the administration of PIP. PIP's ability to scavenge free radicals, such as ROS, provides its antioxidant ability [16]. Both the pleiotropism and favorable safety profile of black pepper (BP) make it a valuable medicinal plant for consumption in multifarious diseases, such as AD and associated cognitive decay. Since *Piper nigrum* and its' constituents such as PIP and BCP interact with several molecules involved in these pathways, it may be a capable herb for treatment/prevention of cognitive decline. Therefore, this systematic review aims to provide an overview of pre-clinical and clinical studies that have examined how black pepper affects cognitive enactment in AD and non-pathological senescence.

2. Methods

This systematic review was conducted according to the established PRISMA guidelines [17]. A literature search was directed on the electronic databases of Scopus, PubMed, Embase, ProQuest, and Web of Science. The search was passed without time limitation using following search strings in the title/abstract/keywords: "piper nigrum" OR piperine OR "black pepper" OR β-caryophyllene OR beta-caryophyllene AND "Alzheimer's disease" OR dementia OR amnesia OR memory OR cognitive OR cognition OR nootropic. Retrieved articles were imported to EndNoteX6. All articles were independently screened for, duplicity and eligibility by authors separately.

Inclusion criteria were: I) original research, II) published in English, III) use of any form of *piper nigrum* and its' major constituents (PIP, BCP), IV) studies with sufficient results, and V) published and in press articles before 18 January 2020.

Articles were excluded if I) the study did not evaluate AD, cognitive disorders, and any related conditions, II) no related tests were used III) piperine was used as bioavailability enhancing agent IV) only abstract was available V) the article was a review, a case report, not-randomized clinical trials, in vivo studies without any cognitive measurements, an in-vitro, and in-silico study. Regarding these articles, the authors individually extracted and categorized data on the characteristics of the animal model of study, sample size, targeted compound, the dose of treatment, route of administration, duration, and major outcomes for in-vivo studies; and the type of trial study, the patients, and dose of treatment, trial duration, and trial outcomes. (Fig. 1) illustrates a diagram of the study selection process. In total, the search yielded 353 articles of which 44 met inclusion criteria (Fig. 1). In total, 35 preclinical studies evaluating AD, other cognitive disabilities due to neuronal disturbances, and examining healthy cognition performance were included. Study characteristics are depicted in (Table 1, 2).

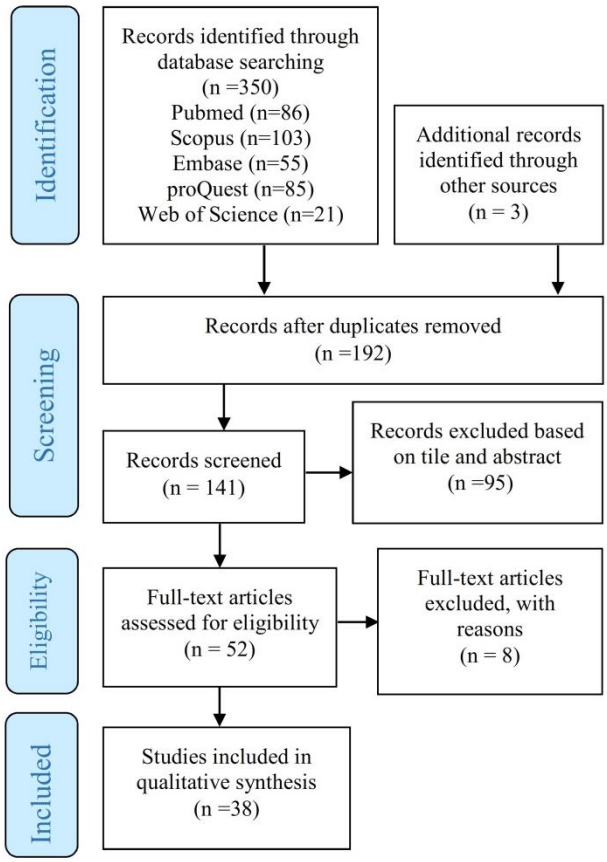

Figure 1. Flowchart describing the study design process based on PRISMA guidelines.

3. Results and Discussion

A total of 353 articles identified following the initial search of databases. Of these, 315 articles were excluded and only 38 articles were included in the present systematic review reporting preclinical and clinical studies on the therapeutic potential of *Piper nigrum* on cognition impairment in Alzheimer's disease and other biological conditions of memory loss. A flowchart, shown in (Fig. 1), depicted the study process. Additionally, (Table 1) and (Table 2) shown the major results of in vivo studies and clinical trials. Impressively, most of the studies were carried out on behavioral examination according to cognition measurements, inflammatory factors, oxidative damage kits, Aβ formation, tau protein sedimentation, autophagy, cholinesterase inhibition, and also histological, morphological and pathophysiological assays. Remarkably most of the studies shown PN's efficiency due to various pathways.

This is the first systematic review of *Piper nigrum* supplementation and its association with AD and cognitive function. Dysfunction of memory is one of the most disabilities of neurological diseases such as strokes, hypoxia, head injuries, depression, anxiety, and neurodegenerative diseases which may cause usual daily activity impairments [1]. BP and its major active components of fruits and essential oils stated as; PIP and BCP could be helpful for treatments of neurodegenerative problems accompanying memory deficit. In this study, we reported the use of *Piper nigrum* and its major constituents in 38 studies that investigated its use in human and in vivo models for AD, and other cognitive impairments which demonstrated promising results. Extracellular sedimentations of the beta-amyloid peptide and the intracellular gathering of hyperphosphorylated tau protein are the main hallmarks of AD [56-58]. Cognitive decline, caused by the accumulation of Aβ plaques and NFTs, is obvious in an anterior-posterior manner, from memory and exclusive functioning to learning deficits [58]. However, the underlying mechanism inducing these protein aggregates remains elusive. Currently, no pharmacological treatment is available to ameliorate the symptoms of the disease [59]. According to PN binding Aβ plaques, decreasing their neurotoxicity and commencing their degradation. Therefore, it is considered a promising therapeutic agent for altering the cognitive symptoms of AD, as evident by the excess of preclinical studies examining its efficacy. In vivo studies have also shown the protective effect of PN in tests that evaluated behavioral activities in mice, where most of these studies used Morris Water Maze (MWM), which is a well-established behavioral test for assessing memory and learning. Other memory experimental examinations were also used such as; Elevated Plus Maze (EPM), Novel

Object Recognition Test (NORT), Passive Avoidance Test (PAT), T-Maze, Y-Maze, Olfactory Function (OF), Holeboard (HLB), Open-Field Test (OFT), Radial Arm Maze (RAM), Object Recognition Test (ORT), Fear Conditioning (FC), Contextual Fear (CF), Fear Extinction Learning (FEL), Cue Dependent Memory Test (CDMT), and Pole Climbing Test (PCT). Most of the studies conducted by These scientists using cognition measurement assessments found that there are declining observations in Escape latency (EL), immobility time, number of errors, and Transfer latency (TL), otherwise, there are increasing detection in exploratory behavior, Retention latency (RL), Time spent in the target quadrant (TSTQ), cognitive performance, time to spend in the open arm, and number of entries to open arm; which show cognition improvement [60-62]. As previously reported in the literature, experiments performed in vivo and clinical trials with AD models (Table 1, 2) show that Aβ plays a causal role in the pathogenesis of AD. Aβ peptides' accumulation leads to the construction of senile plaques, in addition to oxidative damage to the neuron, neuroinflammation, apoptosis, and cognitive insufficiencies. Evidence shows that neurotoxicity induced by intracellular Aβ is partially caused by the increased production of ROS, which leads to oxidative stress. Oxidative stress might influence Aβ production through interaction with amyloid precursor protein [63, 64]. As shown in Table 1, several studies investigated the ability of *Piper nigrum* in eliminating free radicals, where it significantly reduced the ROS and suppressed apoptosis after its supplementation. One of the mechanisms involves a decrease in the toxicity and formation of ROS due to the ability of *Piper nigrum* in potentiating the cellular defense system, stated as increasing the activity of superoxide dismutase (SOD) and catalase (CAT). Therefore counteract the fluctuation in levels of factors associated with the formation of oxidative damages will lead to suppressing the apoptosis, so dampening Malondialdehyde (MDA) and nitric oxide (NO), though increasing SOD, CAT, glutathione (GSH), and Total Antioxidant Capacity (TAC) are part of the treatment approach in AD. Also, tissues obtained post-mortem from AD patients confirmed oxidative damage induced by Aβ [64]. These results corroborate the findings as they hypothesize that BP treatment may play a protective role through the reduction of ROS levels in cultured neurons by a significant regulation of superoxide oxidase and catalase activities, with consequent inhibition of oxidative damage, as well as decline DNA damages. Reactive oxidative stress formed due to activity of the machine of the cell may in turn act at different levels and impair mitochondrial utility, activating the caspase family proteins and causing loss of mitochondrial membrane probability as well as deregulation of the MAPKs and AKT pathways. As previously reported, exposure of cells to 10µl of Aβ for 24 hours significantly activated caspase-3, 8, and 9, whereas pre-treatment with BP lessened its activations and regulation of AKT and some other related pathways. Similar results were also observed regarding the protective effect of PN in regulating the activity of these pathways. Corroborating with these studies, also showed a protective effect of PN resulting from the neutralization of caspase-3 and AKT. A wide variety of TNF-activating cell signaling pathways, including JNK, MAPK, and PI3K AKT, have shown to be regulated by PN. According to PN capacity of binding or directly blocking TNF production and be involved in pro-inflammatory pathways related to most chronic diseases. Modify the production of brain-derived neurotrophic factor (BDNF) plays a specific role in cognitive loss [16]. Besides, the protective effect of *Piper nigrum* against age-associated dementia and Alzheimer's is mediated via suppression of amyloid plaque formation and increasing its clearance, induction of autophagy, attenuation of mitochondrial dysfunction, and regulation of apoptosis. Likewise, some clinical studies have reported that BP possesses the preventive and therapeutic effect on cognitive decline and dementia, which might thus be listed as an additional neuropsychological therapeutical function of this dietary supplement. Piperine can meaningfully raise ChAT activity related to inhibiting the activity of GSK-3β. Additionally, the hyperphosphorylation of tau protein subsequently chronic D-Gal exposure can not only associated with the activated GSK-3β but also contribute to the oxidative damages. Therefore the relationship between dampening the oxidative factors such as; SOD, MDA, NO, DPPH, FRAP, GSH, TAC, etc could be the consequence to ameliorate cognitive impairments. TNF-α may be a strategic downstream signal transducer that is shown in the proinflammatory action of GSK-3β in microglia which can mediate neuroinflammation process over modulation of NF-κB. These discoveries point out that GSK-3β activity is critical for the modulation of neuroinflammatory agents. Diminution of the microglia-mediated inflammatory reaction by GSK-3β inhibition may provide a hopeful approach for the prevention of neurodegeneration and cognitive deficiency. Besides, uncontrolled phosphorylation of tau protein and misfolding in tauopathies and inflammatory in neural processes perform accompaniment in the progress of senescence-related disease pathogenesis. Moreover, previous studies have specified that PIP can increase BDNF expression and protect chronic-stress-induced hippocampal neurodegeneration. overactivity in the M1 microglia phenotype is accompanying the making of ROS and the excretion of proinflammatory cytokines, which conduce neurotoxicity and degeneration [20, 34, 49, 51]. In contrast, the anti-inflammatory M2 phenotype

microglia stimulates tissue healing and extracellular matrix reform. PIP could inhibit neuronal inflammation and apoptosis induced by lowering the level of caspase-3 [65, 66]. This study demonstrated for the first time the role of BCP in alleviating the HFFD-induced metabolic and psychological changes through CB2R activation. BCP improves depression and memory deficit by modulating PGC-1α/BDNF pathway in a CB2R-dependent manner in PFC. Both CB2R and PPAR-γ are involved in the anti-inflammatory, anxiolytic and anti-oxidant effects of BCP. To our knowledge, this is the first study that proposes the upregulation of PGC-1α as the mechanism by which BCP (as a CB2R agonist) activates PPAR-γ. BCP decreases IL-23 levels, a cytokine belonging to the IL-12 family, and appears to reverse age-related cognitive decline in hippocampal-dependent working memory. Beta-caryophyllene appears to be worthy of further study as a treatment to ameliorate the effects of aging through inhibition of the IL-12 cytokine family. Notably, BCP alone did augment the number of astrocytes and their total number of intersections. BCP reverts the detrimental changes in astrocytes and DNA oxidation induced by chronic GAL administration. BCP as a CB2 receptor agonist might be clinically useful as an adjunct treatment in SE to reduce oxidative stress, neurotoxicity, and cognitive impairments [19, 23, 32, 43, 67].

4. Conclusion

We have considered 3 clinical trials of preparations containing black pepper, results indicated some of the positive points in administration of them, but because of the lack of RCTs, and by the effective potential of PN as stated by researchers in in-vivo studies, setting up some RCTs in this field of study would be worthful.

Results of toxicological studies on BP, PIP, and BCP mostly highlighted the safety of the prepared formulations on the liver and kidneys. Also, the protective effect of Piper nigrum against age-associated dementia and Alzheimer's is mediated via dampening factors affecting oxidative damage, mitigating neuroinflammatory agents, a clampdown of amyloid plaque formation and aggregate its clearance, induction of autophagy, attenuation of mitochondrial dysfunction, and regulation of apoptosis.

To conclude, most of the animal studies shown the positive effects of BP, PIP, and BCP on AD and some other causes of cognitive impairments. Further randomized, clinical trials with greater sample size, homogenous test, and tasks of cognitive or memory function, as well as longer duration of treatment and follow-up are compulsory to achieve more conclusive results. Besides, it is suggested to conduct future clinical trials by evaluating *Piper nigrum* products with improved pharmacokinetic properties.

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Conflict of interest

None.

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Table 1. Studies investigating animal models of cognitive impairments.

Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA[1]	Used Part	Duration	Tests	Major Outcomes	Ref.[2]
Wang et al. (2020)	D-Gal[3]	mouse	N[4]=125, (5 groups with 25 mice in each group), 1; CR[5], 2; D-Gal, 3, 4, 5; D-Gal + PIP (2.5, 5, 10)	i.p.[6]	PIP[7]	28 days	MWM[8]	↓EL[9], ↑TSTQ[10], ↓AchE[11], ↑ChAT[12], ↓MDA[13], ↑GSH[14], ↓IL[15]-1β, ↓IL-6, ↓TNF[16]-α, ↓inhibition of PI3K[17]-AKT[18], ↑PKC[19], ↓p-tau202/205, ↑GSK-3[20]β, ↑NF[21]-κB,↑Nrf2[22]	(18)
Youssef et al. (2019)	HFFD[23]	rat	N=40,(5 groups with 8 rats in each group) 1; CR , 2; HFFD, 3; HFFD+BCP (30),, 4; HFFD + AM630[24] + BCP(30), 5; HFFD + BADGE[25]+BCP (30)	p.o.[26]	BCP[27]	4 weeks	EPM[28], OFT[29], Y-maze	↓visceral fat index, ↑spontaneous locomotor activity, ↑exploratory behavior, ↑entry frequency and time, ↓immobility time, ↓FBG[30],↓fasting insulin, ↓HOMA-IR[31], ↑TAC[32], ↑GSH, ↓MDA, ↓NO,↓TNF-α, ↓NF-κB, ↓iNOS[33], ↓PGC-1α[34], ↓BDNF[35], ↓PPAR-γ[36] in PFC[37]	(19)
Wang et al. (2019)	STZ[38]	mouse	N=60 (6 groups with 10 mice in each group), 1; sham, 2;CR, 3;STZ , 4, 5, 6; STZ + PIP (2.5, 5, 10)	i.p.	PIP	23 days	MWM, OFT	horizontal and rearing activities=> NSD[39], ↓learning ability, ↓cognitive deficiencies, ↓EL, ↑TSTQ, ↑NE[40], ↑DA[41], ↑5-HT[42] in the hippocampus, ↑GABA[43], ↓glutamate, ↓MDA, ↑SOD[44], ↑CAT[45], ↑GSH, ↓NO[46], ↓M1 markers' expression (CD86 and iNOS), ↑M2 markers expression (ARG1 and CD206), spontaneous locomotor activity=>NSD,↓ IL-1β, ↓IL-6, ↓, TNF-α, ↑ IL-4, ↑IL-10	(20)
Maneenet et al. (2019)	UCMS[47]	Mouse	N=44(5 groups) و1 ; CR (n=8), 2; UCMS, 3; UCMS + vitamin E (100) (n=10), 4, 5; UCMS + KBD[48] (100, 500) (n=8 per each)	p.o.	PN[49] in a complex	3 weeks	Y-maze, NORT[50]	↑spontaneous alternation performance, ↑time exploring the novel object, ↑discrimination performance, Serum CORT[51]=>suppressed, ↓MDA, ↑CAT, ↑SOD	(21)

[1] Route of Adminstration
[2] Reference
[3] galactose
[4] number
[5] control
[6] intraperitoneal
[7] piperine
[8] Morris Water Maze
[9] Escape Latency
[10] Time spent in the target quadrent
[11] acetylcholinesterase
[12] Choline Acetyl Transferase
[13] Malondialdehyde
[14] Glutathione
[15] interleukin
[16] Tumor necrosis factor
[17] Phosphatidylinositol-3-kinase
[18] Protein kinase B
[19] Protein kinase C
[20] Glycogen synthase kinase 3
[21] Nuclear factor
[22] nuclear factor erythroid 2-related factor 2
[23] High fat fructose diet
[24] 6-Iodopravadoline
[25] Bisphenol A diglycidyl ether
[26] Per os (orally)
[27] Betacaryophylen
[28] Elevated Plus Maze
[29] Open Field Task (Test)
[30] Fasting blood glucose
[31] Insulin resistance
[32] Total antioxidant capacity
[33] Inducible nitric oxide synthase
[34] Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
[35] Brain-derived neurotrophic factor
[36] Peroxisome proliferator activated receptor-γ
[37] Prefrontal cortex
[38] streptozotocin
[39] No significant difference
[40] norepinephrine
[41] dopamine
[42] 5-hydroxytryptamine
[43] γ-Amino butyric acid
[44] Superoxide dismutase
[45] catalase
[46] Nitric oxide
[47] Unpredictable Chronic Mild Stress
[48] Kleeb Bua Daeng
[49] Piper nigrum
[50] Novel Object Recognition Test
[51] corticosterone

Table 1. Studies investigating animal models of cognitive impairments.

Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA	Used Part	Duration	Tests	Major Outcomes	Ref.
Lindsey et al. (2019)	Aged	mouse	N=21 (3 groups) 1; 3 months mice, 2; 12 months mice, 3; 18 months mice, Monday /Wednesday/Friday (100, 178, 300)	i.p.	BCP	3 weeks	Y-maze	↑No.[52] of spontaneous alternations, ↓IL-23, ↓IL-27, ↓IFN[53]-β	(22)
Chavez-Hurtadoet al. (2019)	D-Gal	mouse	N=40 (4 groups with 10 mice in each group), 1; CR, 2; BCP (10) , 3; D-GAL , 4; D-GAL+BCP (10)	p.o.	BCP	8 weeks	OFT, MWM	total distance and their active time=> NSD ,TSTQ=>NSD, ↓CA3, CA1=> NSD, ↓dPFC, ↓oxidation through 8-oxo-dG immunostaining	(23)
Tchekalarva et al. (2018)	KA[54]	mouse	N=48 (6 groups with 8 mice in each group), 1; CR , 2; KA+DZP[55], 3; KA+Phenytoin Sodium, 4, 5, 6; KA+BCP (30, 100, 300)	i.p.	BCP	7 days	MWM	↑spatial learning capacity, ↓EL, ↑TSTQ, ↓lipid peroxidation, ↓seizure scores	(24)
Shelar et al. (2018)	Aβ25-35	rat	N=104, (13 groups with 8 rats in each group), 1; CR, 2; Sham, 3; veh[56], Experimental groups with Aβ25-35 peptide: 4, 5, 6; SG[57] l[58] (100), SG m[59] (200) , SG h[60] (400), 7, 8, 9; EE[61] l (100), EE m (200), EE h (400), 10, 11, 12; LE[62] l (100), LE m (200), LE h (400), 13; Donepezil	p.o.	PN in a complex	21 days	MWM, RAM[63]	↓EL, ↑TSTQ, ↑memory, glucose, total protein, albumin, AST[64], ALT[65], triglycerides, cholesterol, HDL[66], folic acid, Alk-P[67]=>NSD, ↓amyloid plaques formation, ↑SOD, ↑GSH, ↑CAT, ↓MDA, ↓NO, ↑NE, ↑DA, ↑5- HT, ↓AchE activity, ↑BDNF	(25)
Pandit et al. (2018)	Thermogenesis	rat	N=80, (2 groups with 40 rats in each group), R[68]T, CT[69]; subdivided into 4 groups ;(n=10)1; CR, 2; green tea, 3; BP, 4; cinnamon	p.o.	BP	7 days	NORT	↑memory, ↑cognitive performance, NE, FFAs[70], ↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑UCP[71]1 expression in BAT[72], BDNF expression=> NSD	(26)
Khalili-Fomeshi et al. (2018)	STZ	rat	(12 groups);treatment: 1; CR , 2; sham CR; NS[73]/tween 80, 3; sham CR; NS/PIP (5) , 4; (negative CR); STZ/tween, 5, 6, 7; tween 80 +PIP (2.5, 5, 10), 8; (positive CR); STZ/memantine), Pretreatment: 9; tween 80, 10, 11, 12; tween 80 + PIP (2.5, 5, 10)	i.p.	PIP	3 weeks	RAM, PAT[74]	behavioral parameters=> NSD, WM[75]=> NSD, ↓no.of errors, no. of adjacent arm choices=>NSD, ↑time is taken to visit each arm (cognitive ability), ↓MDA, ↑FRAP[76], ↑distribution of CV-positive neurons	(27)

[52] number
[53] interferon
[54] Kainic acid
[55] diazepam
[56] vehicle
[57] Sarasvata ghrita
[58] low
[59] medium
[60] high
[61] Ethanolic extract
[62] Lipid extract
[63] Radical arm Maze
[64] Aspartate aminotransferase
[65] Alanine aminotransferase
[66] High density lipoprotein
[67] Alkaline phosphatase
[68] Room temperature
[69] Cold temperature
[70] Free fatty acids
[71] Uncoupling protein
[72] Brown adipose tissue
[73] Normal saline
[74] Passive Avoidance Test
[75] Working memoru
[76] Ferric reducing antioxidant power

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Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA	Used Part	Duration	Tests	Major Outcomes	Ref.
Etman et al. (2018)	Colchicine	rat	N=36, (6 groups with 6 rats in each group), 1; (negative CR); ACSF[77], 2; (positive CR); colchicine, 3;blank ME[78],, 4; PIP suspension (2.5) +MC, 5; PIP-loaded W/O ME (2.5 mg), 6; PIP-loaded O/W ME (2.5)	p.o.	PIP	21 days	PAT	↑training latency, RL[79], ↑cognitive performance, ↑SOD, ↓MDA, ↑TAC, ↓AchE, organomegaly=>NSD, ↓food and water intake, ↓body weight, ALT level=>NSD, ↑AST, ↑serum urea and creatinine, ↓caspase-3 activity, ↓TNF-α	(28)
Dahiya et al. (2018)	Physostigmine	mouse	(8 groups)1; NS, 2; physostigmine , 3; EGCG[80] (25) ,4; EGCG (25) loaded nanosuspension, 5; EGCG (25)-PIP (5) nanocomplex , 6; blank nanosuspension (25), 7; PIP (5), 8; NS	i.p.	PIP	21 days	MWM, EPM	↓TL[81], ↓EL, ↑TSTQ, spontaneous locomotor activity scores=>NSD, ↓AchE	(29)
Rinwa et al. (2017)	CUM	mouse	(9 groups with 8-10 mice in each group), 1; no stress , 2; CUS[82]+veh , 3, 4, 5; CUS+Que[83] (20, 40, 80), 6; CUS+PIP (20), 7, 8: CUS+Que (20, 40) +PIP (20) , 9; CUS+piracetam	p.o.	PIP	28 days	MWM, EPM	↓TL, ↓EL, ↑memory and learning performance, ↑TSTQ, ↓MDA, ↓NO, ↑GSH, ↑SOD, ↑CAT, ↓AchE, ↓CORT, ↓TNF-α	(30)
Mao et al. (2017)	pilocarpine	rat	N=24, (3 groups with 8 rats in each group), 1; NS, 2; pilocarpine + NS, 3; pilocarpine + PIP (40)	p.o.	PIP	45 days	MWM	↓%status epilepticus, ↓EL, ↓TNF-α,↓ IL-1β, ↓MDA, ↑GSH, ↑SOD, ↑CAT, ↓caspase‑ 3 activity, ↓Bax/Bcl-2[84] signaling pathway	(31)
Lou et al. (2017)	VD[85]	rat	N=84 (5 groups); 1 (sham), 2 (2VO); NS; HPβCD, 3, 4, 5; HPβCD/BCP (144, 48, 16)	i.p.	BCP	50 days	MWM	↓EL, ↑memory and learning performance, ↑TSTQ, ↑spatial learning and memory, ↑CBF recoveries, ↓no. of abnormal neurons, ↑expression of the CB2 in the corona radiata, pyramidal tract and hippocampus, ↑expression of the P13K, p-Akt, and CB2	(32)
Kamila et al. (2017)	N.M.[86]	rat	N=8, (2 groups with 2 rats in each group),1; CR; vehicle, 2; standard; Bacopa monnieri (50), 3, 4; treatment; FM5[87] (50, 100)	p.o.	PN in a complex	24 h	EPM	↓TL, ↓EL, ↑memory and learning performance	(33)

[77] Artificial Cerebrospinal Fluid
[78] microemulsion
[79] Retention latency
[80] Epigallocatechin gallate
[81] Transfer latency
[82] chronic unpredictable stress
[83] quercetin
[84] B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax)
[85] Vascular dementia
[86] Not mentioned
[87] Herbal preparation

Table 1. Studies investigating animal models of cognitive impairments.

Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA	Used Part	Duration	Tests	Major Outcomes	Ref.
Iqbal et al. (2016)	AlCl3	Mouse	N=30, (3 groups with 10 mice in each group), 1; CR; water + standard diet, 2; AlCl3, 3; AlCl3 + BP	p.o.	BP	30 days	MWM, EPM	↓EL, ↑TSTQ, ↑time in exploring the platform, time spent in the open arm, ↑no. of entries to open arm, ↑freezing response (FC), ↓freezing response (FEL), ↑spending time with another mouse, ↑interaction time with a stranger mouse, ↓APP[88]770 expression in the hippocampus, APP695 expression in amygdala=>NSD, ↑%inhibition of DPPH[89] free radicals in hippocampus, cortex, and amygdala	(34)
de Oliveira et al. (2016)	PTZ[90]	mouse	N=16, (2 groups with 8 mice in each group), 1; CR; Veh, 2, 3, 4; BCP (10, 30, 100)	i.p.	BCP	60 min	OFT, ORT	Onset latency, duration of the first generalized tonic-clonic seizure=>no significant change, EEG =>NSD, no. of crossings, rearing, or time spent in the center, the latency to fall off the rod, immobility time, total time spent in object exploration=> NSD, ↑values of object recognition index, TBARS[91] in the cerebral cortex, NPSH[92] in hippocampus=>no significant changes	(35)
Yang et al. (2015)	MPTP[93]	mouse	N=27, (3 groups with 9 mice in each group), 1; CR; NS, 2; PIP (10)+MPTP 3; MPTP	p.o.	PIP	15 days	MWM	↑Latency to fall off the rotating rod, ↓ EL, MPTP-induced dopaminergic neuronal death in the SNpc[94]=>protected, IL-1β expression=>suppressed, ↓no. and morphological phenotype of activated microglia, ↑SOD, ↓MDA, ↑Bcl-2 expression, ↓Bax expression	(36)
Subedee et al. (2015)	AlCl3	rat	N=24, (4 groups with 6 rats in each group), 1; CR; propylene glycol, 2 ; AlCl3, 3; AlCl3 + PN (20), 4; AlCl3+ PN (200)	p.o.	PN	2 months	MWM	↓Brain cholinesterase level, ↓EL,↑TSTQ, β-amyloid plaques=>not observed, morphological disturbance=>NSD	(37)
Hritcu et al. (2015)	Aβ (1–42)	rat	N=60, (6 groups with 10 rats in each group), 1; CR; sham; distilled water, 2; Aβ (1–42) + DZP, 3; Aβ (1–42) + TRM[95], 4; Aβ (1–42) + distilled water, 5; Aβ (1–42) + PN (50), 6; Aβ (1–42) + PN (100)	p.o.	PN	21 days	EPM	↑time spent in the open arms,↑ no. of open-arm entries, ↑no. of crossing (exploratory activity), ↑swimming time, i↓mmobility time, ↑SOD, ↑GPX[96], ↑CAT, ↓MDA, ↑GSH, ↓protein carbonyl level, DNA cleavage patterns=>absent	(38)

[88] Amyloid precursor protein
[89] 1,1-diphenyl-2-picrylhydrazyl
[90] pentylenetetrazol
[91] Thiobarbituric acid reactive substance
[92] non-protein sulfhydryls
[93] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
[94] substantia nigra pars compacta
[95] tramadol
[96] glutathione peroxidase

Tabe 1. Studies investigating animal models of cognitive impairments.

Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA	Used Part	Duration	Tests	Major Outcomes	Ref.
Elnaggar et al. (2015)	Colchicine	rat	N=48, (8 groups with 6 rats in each group),1; Negative CR; ACSF, 2; Positive CR; colchicine, 3; i.n. blank CS-NPs[97], 4; i.n. freshly prepared PIP solution (0.250) in PG[98] (0.045), 5; i.n. freshly prepared PIP solution (0.250) in PG (0.250), 6; i.n. PIP-loaded CS-NPs (0.045), 7; i.n, PIP-loaded CS-NPs (0.250) 8; donepezil	i.n.[99]	PIP	21 days	MWM	↓EL, ↑RT[100], ↓AchE, ↓MDA, ↑TAC, ↑SOD, ↓caspase-3 activity, ↓TNF-α value	(39)
Elnaggar et al. (2015)	Colchicine	rat	N=42, (7 groups with 6 rats n each group),1; Negative CR; ACSF, 2; positive CR; colchicine, 3; blank cubs-colchicine, 4; PIP-cubs-colchicine (2.5) ,5; PIP-T-cubs-colchicine (2.5), 6; PIP-S mix cubs-colchicine(2.5), 7; PIP suspension-colchicine injected (2.5)	p.o.	PIP	21 days	PAT	↑RL, ↓AchE, ↓MDA, ↑TAC, ↑SOD, Physical observation=>showed no signs of toxicity (eg, skin, fur, eyes, mucous membrane changes, tremors, sleep, and coma organomegaly or other gross organ changes=>were not observed,↑ food and water intake, ↑body weight, ALT, AST, AST: ALT ratio=>NSD, Urea, Creatinine=>NSD, ↓caspase-3 activity, ↓TNF-α value	(40)
Pragnya et al. (2014)	VPA[101]	mouse	N=30, (5 groups with 6 mice in each group), 1; negative CR; Tween 80 2; PIP, 3; VPA+Tween 80, 4; VPA+PIP (5), 5; VPA+PIP (20)	p.o.	PIP	28 days	MWM, EPM	↓latency to reorient 180˚, ↓latency to paw withdrawal, ↓locomotor activity in actophotometer, ↑latency to fall from rotating rod, ↑time spent in open arms, ↑no. of entries into open arms, ↑no. of social explorations, ↓EL, ↑GSH, ↓MDA, ↓NO, ↓Hippocampal serotonin, ↑no. of Purkinje cells, ↓histopathological alterations	(41)
Hritcu et al. (2014)	Aβ (1-42)	rat	N=40, (4 groups with 10 rats in each group), 1; CR; sham; distilled water, 2; Aβ(1–42) + distilled water , 3; Aβ(1–42) + PN (50), 4; Aβ(1–42) + PN (100)	p.o.	PN	21 days	Y-maze, RAM	↓%Aβ plaque load, no. of arm entries=> NSD, ↑%spontaneous alternation ,↑WM, ↑reference memory, ↑SOD, ↑GPX, ↑CAT, ↓MDA, ↑GSH, ↓protein carbonyl, DNA cleavage patterns=>absent	(42)
Cheng et al. (2014)	Tg APP/PS1	mouse	(7 groups), 1; CR, 2; APP/PS1, 3, 4, 5; APP/PS1 BCP (16, 48, 144), 6; APP/PS1+AM630+BCP (48), 7; APP/PS1+GW9662+BCP (48)	p.o.	BCP	10 weeks	MWM	↓EL, ↓Escape distance, ↑TSTQ, swimming speed (velocity)=>NSD, ↓Aβ deposition, activation of astrocytes=>suppressed, ↓Iba-1 protein expression, ↓COX-2, ↓mRNA levels of TNF-α, IL-1β, ↑mRNA levels of IL-10	(43)

[97] Chitosan Nanoparticles
[98] propylene glycol
[99] intranasal
[100] Retention time
[101] Valperoic acid

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Borre et al. (2014)	OBX[102]	rat	N_1=48 (4 groups with 12 rats in each group), 1; CR; CR-diet, 2; Exp[103]-diet, 3; OBX+CR-diet, 3; OBX+Exp-diet N_2=40 (4 groups with 10 rats in each group), 1; CR; Veh, 2; memantine+Veh, 3; OBX+Veh, 4; OBX+memantine N_3=24 (2 groups with 12 rats in each group), 1; NS , 2; $ZnSO_4$	p.o.	PIP in a complex	28 days	OFT, PAT, T-maze,	↓spatial memory deficit in T-maze, ↑fear memory loss in PAT, spatial memory deficit=>failed, Hyperactivity=>normalized, changes in the hippocampal weights↓, cell loss in the hippocampus=>partially rescued, rescuing in CA3, CA1 dorsal hippocampus=>failed, DG=>rescued, cell loss in the CA3, CA1, and DG=>rescued, ↓Splenic T-cells, ↑% ((n-3) FAs EPA and DHA), ↓(n-6) FA, ↓AA in the total phospholipid FAs	(44)
Banji et al. (2013)	D-GAL	rat	N=42, (7 groups with 6 rats in each group),1; CR; MC[104], 2; naturally aged rats+ MC, 3; D-GAL, 4; D-GAL+CMN[105] (40), 5; D-GAL + PIP (7.5), 6; D-GAL+CMN (20)+PIP (7.5), 7; D-GAL+CMN (40)+PIP (15)	p.o.	PIP	56 days	EPM	↑No. of entries in open arms, ↑TL, ↑time spent on the rotating rod, ↑FRAP, ↓NO, ↓protein carbonyl, ↓AOPP[106], ↑thiol levels, ↓4-hydroxynonenal, structural integrity and architecture of Purkinje cells=>improved	(45)
Banji et al. (2013)	D-GAL	rat	N=42, (7 groups with 6 rats in each group),1; CR; MC, 2; naturally aged rats+MC, 3; D-GAL, 4; D-GAL+CMN (40)+MC, 5; D-GAL+PIP (7.5)+MC, 6; D-GAL+CMN (20)+PIP (7.5)+MC, 7; D-GAL+CMN (40)+PIP (15)+MC	p.o.	PIP	49 days	MWM	↓EL, ↑No. of crossings, ↑hippocampal volume and no. of neurons in the CA1 region, ↑SOD, ↑CAT, ↓MDA, ↑GSH, ↓lipofuscin like AFS, ↑serotonin, ↑histological features of the CA1 region of the hippocampus	(46)
Rinwa et al. (2012)	CUS	mouse	(9 groups), 1; CR, 2; CUS , 3; CUS+CMN (100), 4; CUS+CMN (200), 5; CUS+CMN (400), 6; CUS+PIP (20), 7; CUS+CMN (100)+PIP (20), 8; CUS+CMN (200)+PIP (20), 9; CMN (100)	p.o.	PIP	28 days	EPM, MWM	↑locomotor activity, ↑sucrose consumption, ↓initial transfer latency, ↓retention transfer latency, ↑TSTQ, ↓EL, ↓MDA, ↓NO, ↑GSH, ↑SOD, ↑CAT, ↓Brain AchE, ↑Complex I, II, III, IV, ↓CORT	(47)
Head et al. (2012)	Aged	dog	N=15; Treatment (n=8), CR (n=7); CR capsules were formulated without any of these active ingredients. Dogs were given two capsules per day, one in the morning before cognitive testing and one in the afternoon.	p.o.	PN in a complex	9.4 months	N.M.	↓Errors to criterion, ↑accuracy, oddity discrimination=>NSD,Size discrimination, reversal learning, and spatial,memory=> NSD, spatial memory retest=>NSD, ↓CPK[107], Aβ40, Aβ42, total Aβ=>NSD	(48)
Priprem et al. (2011)	N.M.	rat	n = 32, (4 groups with 8 rats in each group), 1; Veh, 2; Blank liposomes, 3; p.o. PIP, 4; i.n. PL[108]	p.o., i.n.	PIP	2 weeks	MWM	↓EL, ↑RT, ↑swimming duration, ↓climbing duration, ↓immobility time, grooming behaviors, rearing behaviors, and licking of rats =>spontaneous locomotor activity=> NSD	(49)

[102] Olfactory bulbectomized rat
[103] experiment
[104] Methyl cellulose
[105] curcumin
[106] Advanced oxidation protein products
[107] Creatine phosphokinase
[108] piperine-encapsulated liposomes

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Author (Year)	Model	Animal	Study Design (mg/kg/day)	RoA	Used Part	Duration	Tests	Major Outcomes	Ref.
Parachikova et al. (2010)	Tg[109]2576	mouse	N=30, (3 groups with 10 mice in each group), 1; low dose diet (184), 2; high dose diet (553), 3; CR diet	p.o.	PIP in a cocktail	6 months	MWM, NORT	↓EL, ↑TSTQ, ↑no. of crossings,↑ time spent to explore novel objects, Aβ42=>unchanged, ↓Aβ40, ↓C83, ↓C99, ↓levels of soluble oligomers	(50)
Chonpathompikunlert et al.(2010)	AF64A[110]	rat	N=48 (6 groups), 1; Veh + ACSF, 2; Veh + AF64A, 3; Donepezil + AF64A, 4, 5, 6; PIP (5, 10, 20) + AF64	p.o.	PIP	3 weeks	MWM	↓EL, ↑RT, ↓AchE activity, ↓MDA, neuron density=>improved	(51)
Wattanathorn et al. (2008)	N.M.	rat	N=42 (6 groups), 1; intact CR, 2; Veh 3; positive CR; fluoxetine, DZP, Donepezil, 4, 5, 6; PIP (5, 10, 20)	p.o.	PIP	4 weeks	EPM, MWM	↓immobility time, climbing time=>NSD, ↑swimming time, no. of opened arm entry and time spent in the open arm=>NSD, ↓EL, ↑RT, grooming behaviors, rearing behaviors, and licking of rats=> spontaneous locomotor activity=>NSD	(52)

Table 2. studies investigating RCTs related to cognition.

Author (Year)	Type of clinical trial	population Type	population Number Gender	Targeted compound	Dose	Duration	Investigated outcomes	References
Schneider (2016)	three-armed, randomized, and con- trolled clinical trial	18 to 59 years old	45 participants (34 women)(11 men) During each of the seven 1-minute breaks, participants applied a lipstick-sized inhaler. Participants in the control group did not use an odor inhaler.	AromaStick® (complex including BP)	N.M.	Everyday situations	The inhaler Alert was able to increase cognitive performance by 29% Concentration: Alert%=92; Focus% =84; Control% =62 a sensation of "having one's mind cleared"	(53)
Tajadini et al. (2015)	randomized double-blind placebo-controlled clinical trial	patients older than 50 years of age with MMSE scores between 15 and 26 and mild to moderate Alzheimer's disease	D[111]; 24/25 P[112]; 20/25 P; 50% male P; 50% female D; 50% male D; 50% female	17.5 in a complex of 500 mg	1.5 g daily	12 weeks	↑ADAS-cog[113] ↑CDR-SOB[114] scores	(54)
Lindheimer et al. (2013)	double-blind, randomized, placebo-controlled crossover experiment	ages of 18–34	three orders: rosemary, then pepper (n =14, 9 women), rosemary, then P (n = 13, 10 women), or pepper, then P (n =13, 10 women).	PN in a complex	N.M.	16-minutes	Significant short-term improvements in sustained attention, motivation to do cognitive work, or feelings of mental energy and fatigue in young adults with low energy.	(55)

[109] transgenic
[110] Ethylcholine mustard aziridinium ion
[111] drug
[112] placebo
[113] Alzheimer's Disease Assessment Scale-cognitive subscale
[114] Clinical Dementia Rating Scale Sum of Boxes