Table 1: Molecular interaction of top five lead phytoconstituents with N-methyl-D-aspartate receptor

Phytochemicals	Glide score	Glide energy (kcal/mol)	ΔG_{edw} (kcal/mol)	ΔG_{ecol} (kcal/mol)	Xphbond (kcal/mol)	Interacting residues	Bond length (Å)
DCKA (bound ligand)	−14.08	−43.865	−28.096	−15.769	−3.422	Pro124(H-bond), Thr126(H-bond), Arg131(Two H-bond)	2.33,1.84, 1.87, 1.79
Caffeic acid	−9.25	−33.791	−18.809	−14.981	−3.556	Thr126(H-bond), Arg131(Two H- bond)	1.72, 1.90, 1.65
Cinnamic acid	−8.52	−30.567	−17.515	−13.051	−2.401	Thr126(H-bond), Arg131(Two H-bond)	1.72, 1.88, 1.74
Octanoic acid	−8.49	−28.619	−15.467	−13.152	−2.507	Thr126(H-bond), Arg131(H-bond), Arg131(H-bond)	1.92, 1.91, 1.60
P-coumaric acid	−8.1	−31.665	−15.903	−15.761	−2.713	Thr126(H-bond), Arg131(H-bond), Arg131(Salt-bridge), Trp223(π-π Stacking)	1.71, 1.70, S4.06, 5.23
Decanoic acid	−8.04	−30.821	−17.264	−13.557	−2.36	Thr126(H-bond), Arg131(Two H-bond)	1.89, 1.68, 1.79

DCKA: 5,7-Dichlorokynurenic acid

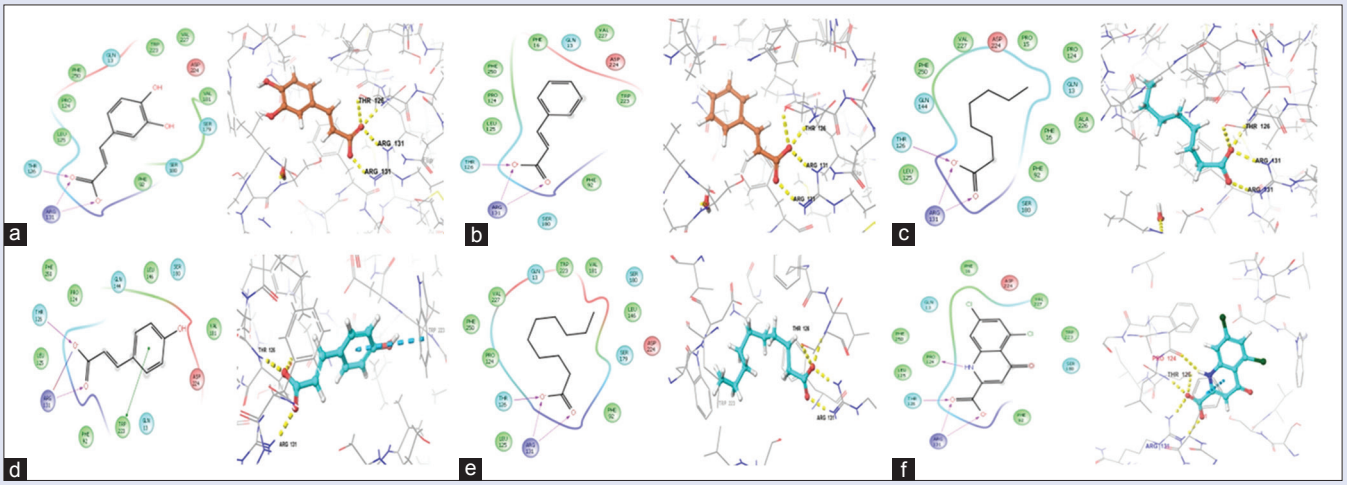

Figure 2: Molecular interaction of top lead phytoconstituents with N-methyl-D-aspartate receptor. (a) caffeic acid, (b) cinnamic acid, (c) octanoic acid, (d) p-coumaric acid, (e) decanoic acid and (f) 5,7-dichlorokynurenic acid (bound ligand)

and octanol-water partition coefficient log $P < 5$. The analysis revealed that none of the phytoconstituent violated the rule except caffeic acid and p-coumaric acid. Their octanol-water partition coefficient was above five though they were still following the Lipinski's rule of five as the drug which was to be formulated orally should have no more than one violation.[27] When predicted for toxicological property all the top five leads were found to be noncarcinogenic in rodent, mouse as well as rat model and nonmutagenic in *Salmonella typhimurium* model [Table 2].

DISCUSSION

AD is a major form of dementia with no curable therapy till date. Different hypothesis, concepts, and theories have been postulated to understand its pathophysiology. The cholinergic and Aβ hypotheses, being the most accepted theories, were not able to provide any asymptomatic treatment for AD.[28] Another hypothesis proposed was "Glutamatergic and Excitotoxic hypothesis," which states the involvement of glutamate-mediated neurotoxicity in the pathogenesis of AD. NMDA receptors are heterotetrameric complexes composed two obligatory NR1 subunits and two NR2 subunits, which can a form a dimer in itself and alternatively with one NR2 or NR3 subunit. NMDA receptors have multiple modulatory sites, NR1 subunit contains a glycine binding site (Gly/NMDA), NR2 subunit contains the glutamate-binding site (Glu/NMDA), a binding site at channel blockers, and allosteric sites on the amino-terminal domain.[29] All these different binding site of NMDA receptor allows various allosteric interactions with different ligands. Previous reports gave main emphasis to the Glu/NMDA of NR2 subunit and channel pore; however, due to their associated side effects, recent emphasis is on developing antagonists at the Gly/NMDA of NR1 subunits, which is also an obligatory part of NMDA tetramer complex.[30]

Plants products and extracts have always been an essential part of traditional medicine and used for the treatment of many diseases including neurological disorder.[31] Due to the diverse and rich source of plant products, herbs and spices have been reported in traditional medicine. In the last decade, researchers have shown the importance of phytoconstituent from spices in preventing neurodegenerative diseases.[32] The dried seeds, fruits, barks, leaves, or roots of plants can be summed up as spices. The rate and occurrence of neurological diseases in western countries are way higher compared to Asian countries (including India), where spices are consumed on daily basis.[33] In India, spices are the integral part of Indian delicacy to impart flavor, color, and used for preservative properties. Curcumin, the principal phytoconstituent of *Curcuma longa L.* (an Indian spice), have neuroprotective effect. Matteucci *et al.*, in 2005, studied the effect of curcumin pretreatment against NMDA-induced apoptosis in rat retinal neurons.[34] It was found that curcumin attenuates NMDA-mediated excitotoxicity by inhibiting phosphorylation of NR1 subunit and NMDA receptor-mediated Ca^{2+} increase.[35] In another study, the water extract of *P. nigrum* L. decreased the amplitude of NMDA-induced depolarization in genetically epilepsy-prone DBA/2 mice, suggesting an antagonist action at NMDA receptors that might be contributing to the anticonvulsant property of *P. nigrum* L. extract.[36] Moreover, spices have already been established to have medicinal properties against various diseases such as diabetes, cancer, inflammations,

Table 2: Molecular descriptor values of top lead phytoconstituents

Phytoconstituent	Molecular weight	Percent human-oral absorption	CNS activity	BBB partition coefficient	QPlogPo/w	SASA	DonorHB	AccptHB	Lipinski's rule
	<500	>80% high, <25% low		−3.0–1.2		300–1000	<5	<10	
Caffeic acid	180.16	54.222	−2	−1.552	9.873	389.443	3	3.5	0
Cinnamic acid	204.355	100	−1	−0.551	−0.045	365.183	0	0	0
Octanoic acid	144.213	84.973	−1	−0.739	3.556	413.495	1	2	0
P-coumaric acid	164.16	67.487	−2	−1.077	7.785	378.002	2	2.75	0
Decanoic acid	172.267	87.028	−1	−0.922	3.275	479.837	1	2	0

Phytoconstituent	Acute toxicity (fathead minnow) (mg/L)	Carcino-genicity (rodent [multiple species/sites])	Carcino-genicity (mouse)	Carcino-genicity (rat)	Carcino-genicity (mouse [TD50]) (mg/kg_bw/day)	Carcino-genicity (rat (TD50)) (mg/kg_bw/day)	Maximum recommended daily dose (human) (mg/kg_bw/day)	Mutagen-city (*Salmonella typhimurium*)
Caffic acid	8.26	Noncarcinogenic	Noncarcinogenic	Noncarcinogenic	4.9	0.297	3.63	Nonmutagenic
Cinnamic acid	6.64	Noncarcinogenic	Noncarcinogenic	Noncarcinogenic	1.43	0.115	-	Nonmutagenic
Octanoic acid	190.0	Noncarcinogenic	Noncarcinogenic	Noncarcinogenic	0.139	0.802	25.2	Nonmutagenic
Coumaric acid	18.3	Noncarcinogenic	Noncarcinogenic	Noncarcinogenic	1.51	0.204	16.0	Nonmutagenic
Decanoic acid	222.0	Noncarcinogenic	Noncarcinogenic	Noncarcinogenic	0.165	0.804	32.5	Nonmutagenic

CNS: Central nervous system; BBB: Blood–brain barrier; SASA: Solvent accessible surface area; DonorHB: Hydrogen bond donors; AccptHB: Hydrogen bond acceptors; QPlogPo/w: Predicted octanol/water partition coefficient; MolPSA: Molecular polar surface area

and cardiovascular diseases. Due to the side effect associated with approved drugs, phytoconstituent has gained enormous importance as an alternative for the treatment of several ailments. In view of this, the phytoconstituent reported from different spices are being explored for NMDA-receptor antagonist properties. The phytoconstituent were selected based on literature information for the following spices, i.e., *P. nigrum* L., *C. zeylanicum* Blume, *E. caryophyllata* Thumb, *C. cyminum* L., and *E. cardamomum* L. Molecular docking tool was used to study molecular interaction and lead identification. Phytoconstituent such as caffeic acid, cinnamic acid, octanoic acid, coumaric acid, and decanoic acid exhibited high docking score and binding energy. Pharmacokinetic properties of lead phytoconstituent were also found to be extremely favorable based on the Lipinski's rule. The lead phytoconstituent, i.e., caffeic acid, a phenolic acid, have already been established to have anticholinesterase activity.[37] Caffeic acid was also studied for the attenuation of Aβ 25–35-induced cognitive impairment and memory deficits through inhibition of lipid peroxidation and nitric oxide production as well as for attenuation of Aβ-induced neurotoxicity on PC12 (pheochromocytoma) cells of rat adrenal medulla.[38] Hence, due to the multipotent effect of these compounds, they are potentially useful in the future for deriving new therapeutic strategy directed against the NMDA receptor as antagonist.

CONCLUSION

Caffeic acid, cinnamic acid, octanoic acid, coumaric acid, and decanoic acid exhibited high docking score and binding energy with the NMDA receptor. Hence, these phytoconstituents can be useful in developing novel NMDA-receptor antagonist which may have therapeutic potential in AD. Further *in vitro* and *in vivo* studies are required to validate the *in silico* results shown in the present study.

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Conflicts of interest

There are no conflicts of interest.

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