Published online in http://ijam.co.in ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 14 (3), 2023; 794-800

Efficacy and safety of *Vicia faba L.* extract compared with levodopa in management of Parkinson's disease and an *in-silico* phytomedicine analysis

Research Article

Karim Nikkhah[1], Ali Shoeibi[2], Fariborz Rezaeitalab[3], Samira Aminzadeh[3], Hussein Sharara[4], Mahdi Abbas-Mohammadi[5], Mohammad Al-attar[6], Mohammadeza Akbari[4], Fereydun Moradi[4], Hasan Rakhshandeh[7], Morteza Saeidi[*]

1. Professor of Neurology, 2. Associate Professor of Neurology, 3. Assistant Professor of Neurology, 4. Resident of Neurology, Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, Iran.
6. Independent Researcher, Manama, Bahrain.
7. Medicinal Plant Research Center, Department of Pharmacology, School of Medicine, Mashhad University of Medical Science, Mashhad, Iran.
8. Department of Neurology, School of Medicine, Mashhad University of Medical Sciences. Qaem Hospital, Shariati Sq., Mashhad, Iran.

Abstract

Background: Parkinson's disease is a chronic degenerative disease of the central nervous system, presently lacks an effective therapy for its complex pathogenesis. Agents containing Levodopa can alleviate its symptoms. Hypothesis *Vicia faba L.* (Fava bean) extract may prove a useful antiparkinsonian agent similar to Levodopa. Methods: Thirty patients with Parkinson's disease, entered into this cross over clinical study. In the first step, each participant received V. faba L. extract containing 106.5 mg of Levodopa. After a wash out period of 7 days, the patients entered the second step during which they received conventional treatment with Levodopa-C tablets. Blood Levodopa were measured 4 hours and 8 hours after each administration. The Movement Disorder Society-Unified Parkinson's Disease Rating Scale was employed to measure the therapeutic effects in each step. Additionally, a docking analysis was performed to distinguish the chemical constituents of the plant and six key mediators actively involved in Parkinson disease. Results: The fava bean extract significantly alleviate all studied end points except for tremor at rest and freezing. Wilcoxon Signed Ranks Test showed that there was not a significant difference between rigidity, rising chair, gait and bradykinesia. Docking results of the herb components and standard ligands, indicating that the antiparkinsonian activity of V. faba could presumably be related to many phytochemicals. Conclusion: This study showed a beneficial effect of V. faba L. similar to Levodopa-C. and better compliance due to lower adverse events.

Keywords: Levodopa, *Vicia faba L.,* Fava bean, Parkinson's disease, Bradykinesia.

Introduction

Parkinson's disease (PD) is the most common cause of parkinsonism, a syndrome characterized by rest tremors, rigidity, bradykinesia, and postural instability(1).

Levodopa was first identified in the seedlings, pods, and beans of the broad bean (*Vicia faba* -VF) by Guggenheim in 1913(2). In 1967, George C. Cotzias reported the positive effect of levodopa on Parkinson's disease, and despite some changes and developments in the form of this medicine, it is still the gold standard treatment of PD today(3,4). *Vicia faba L.* (fava beans, field beans, broad beans, or bell beans, a species of beans - Fabaceae) is native to northern regions of Africa and southwest Asia such as Iran. It has a key place in the traditional nutrition of the Mediterranean, Chinese, Indian, English, Middle Eastern, African and Iranian people[5]. Interest in natural products, particularly plant-based, for the treatment of Parkinson's disease has been growing(2,6).

Levodopa's mechanism of action in improving patients' condition remains unknown. Despite symptomatic treatment, cumulative disability remains a major problem requiring further drug discovery research. Drug development plans, however, are moving towards the concept of multi-target anti-parkinsonian pharmacotherapy instead of mono-dopaminergic therapy (7,8).

Despite the great variety of plants in the world, only a few have had their pharmacological effects studied for antiparkinsonian activity; therefore, there is

*** Corresponding Author:**
Morteza Saeidi
Department of Neurology,
School of Medicine,
Mashhad University of Medical Sciences.
Qaem Hospital, Shariati Sq., Mashhad, Iran.
Email Id: Saeidim@mums.ac.ir

a huge potential in this field for future research on plants and their bioactive compounds (2,6).

The current study aimed to evaluate the efficacy and side effects of *V. faba* L. extract in comparison with levodopa for the treatment of PD patients. In addition, the affinity of the chemical compounds of the plant to the active site of six important proteins involved in Parkinson's disease were assessed using molecular docking analysis.

Materials and Methods

This study is registered at the Iranian registry of clinical trials under number IRCT2013060313570N1.

Preparation of *Vicia faba* extract

In this study, 200 kilogram of crushed fava bean (c.v. Barakat), acquired from a farm approved by the Khorasan Razavi Agricultural and Natural Resources Research Center, was centrifuged first by an industrial centrifuge machine to remove suspended particles and then by a laboratory centrifuge at 10000 RPM (revolutions per minute) for 20 minutes to obtain 40 liters of clear extract.

Plasma samples and *V. faba* extract were analyzed for levodopa using a rapid and selective reversed phase high performance liquid chromatographic method(9), which was modified to achieve better separation, sharper peaks, and shorter retention times for the drug. The liquid chromatography comprised of a model 510 Waters pump (Waters Association, Milford, MA, U.S.A.), a variable wavelength, model 486 Waters UV detector and a U6K, and a Waters sample injection system.

Clinical trials

This cross-over trial was conducted on patients newly diagnosed with PD who had not been taking any medication. Initially, 38 patients from two outpatient clinics were included in the study. Because of protocol violations, 8 patients were excluded, leaving 30 patients (between 51 and 81 years of age) to enter the first step of the study. Parkinson's disease was diagnosed by the presence of at least two of the three principal features of the disease (resting tremor, bradykinesia, rigidity); if there was no resting tremor, patients had to have unilateral onset of symptoms. All participants provided written informed consent to participate. The study was conducted in two steps. In the first step, all patients received *Vicia faba L.* extract (25 ml) in three divided doses in the form of solution at a concentration of 4.260 mg/ml levodopa (documented by HPLC analysis). Levodopa was measured 2 and 4 hours after administration by HPLC assays. After a washout period of 7 days, the patients entered the second step during which they received conventional treatment with Levodopa/Carbidopa 100/10 mg tablets. The blood levels of levodopa in all patients were measured in each step before treatment was administered to assure that the effect of *Vicia faba* no longer existed in the serum. In each step, patients were visited 2 hours, 4 hours, 1 day, and 7days after receiving treatment. In each visit, vital signs and therapeutic and adverse effects of the agent were recorded for each patient. To measure the therapeutic effects, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS, last version: 2008), which is evaluated by interview and clinical observation, was applied. Scores can range from 0 to 176 and include subscales of psychological function, activities of daily living, and motor function. Higher scores indicate more severe illness(10).

Classification criteria

Inclusion criteria

Based on the Modified Hoehn & Yahr Scale, PD subjects taking part in this study were assigned to the middle stage: patients with Modified Hoehn & Yahr Scale stage between 2 and 3.

Exclusion criteria

Based on neurologic examination, laboratory tests (including hepatic enzymes), and MRI findings, all patients diagnosed with Parkinson's plus syndrome, hepatolenticular degeneration (Wilson's disease), cerebellar lesions, hepatic encephalopathy, brain stem injuries, multiple sclerosis, or essential tremor, and other non-PD subjects were excluded from the study. Subjects suffering from serious heart, liver, or kidney disease, multiple organ atrophy, or mental retardation were also excluded from the study. Furthermore, patients with a history of alcohol or drug abuse, allergy to *Vicia faba* or G6PD deficiency (approved by negative "direct antiglobulin test") were removed from the study. Finally, patients who had already participated in another clinical intervention research program were excluded as well.

Interventions

Patients were instructed to provide a brief but precise description of every adverse effect (including nausea, vomiting, dizziness, headache, skin rash, sleep disturbances, or changes in appetite) and record the treatment process in detail. Any patient experiencing a grave adverse event was withdrawn from this trial and provided with symptomatic treatment. The adverse events were recorded in a timely manner.

Molecular docking analysis

Preparation of ligands and targeted enzyme as well as the molecular docking analysis was accomplished on the Glide of Schrodinger package 2016-2(11). The structure file of catechol-O-methyltransferase (COMT), monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B), Parkin E3 ligase, α-synuclein and human adenosine receptor A2A enzymes (PDB IDs: 1H1D, 2BXR, 2V5Z, 4I1H, 1XQ8, and 3UZA, respectively) were retrieved from the Protein Data Bank (PDB) and then prepared on the protein preparation wizard in Maestro by removing the crystallized ligands, all free water molecules, and complex proteins with targets in PDB, followed by energy minimization. The grid box of enzymes was created with the Grid generation application at

particular residues of the proteins obtained from the EZPocket server. The ligands of *V. faba* were obtained from the Dictionary of Natural Products in SDF format.

Statistical analysis

The collected data was analyzed using SPSS software version 21.0. Two-tailed tests with the significance level set at α = 0.05 were applied to compare the results. The data was symbolized as mean ± standard deviation. To compare the difference between before and after treatment within one group, the paired t-test (in case of normal distribution data) or Wilcoxon signed-rank test (in case of abnormal distribution data) was applied.

Results

Clinical trial

All 30 patients completed two phases of the study. Mean age of subjects was 66.53±8.58 years of age.

According to this study, the serum levels of levodopa did not alter significantly 2 hours (p=0.087) or 4 hours (p=0.102) after taking each medication (Table 1).

Table-1: The mean serum level of Levodopa in each group and its comparison

Time after administration	The mean serum level of Levodopa		
	L-Dopa-C	*Vicia faba* extract	P value
2 hours	1.12 ± 2.60	2.29 ± 1.17	0.087
4 hours	2.45 ± 1.30	2.01 ± 0.99	0.102

Wilcoxon signed-rank test results showed that there was no significant difference between rigidity (Z: -0.577, p=0.564), rising chair (Z: -2.333, p=0.20), gait (Z: -1.134, =0.257), or bradykinesia (Z: -0.816, p=0.414) four hours after L-Dopa-C and *Vicia faba* extract consumption. Also, there was no significant change in rigidity (Z: -0.577, p=0.564), rising chair (Z: -1.134 , p=0.257), gait (Z: -1.342, p=0.180), or posture (Z: -1.000, p=0.317) one week after L-Dopa-C and *Vicia faba* extract consumption; however, in comparison with *Vicia faba* extract, L-Dopa-C could significantly reduce tremor at rest (Z: -2.333, p=0.020) and freezing (Z: -2.236, p=0.025) after four hours and tremor at rest (Z: -2.235, p=0.025) and freezing (Z: -2.000, p=0.046) after one week of consumption. (Table 2).

Table-2: Clinical findings according to MDS-UPDRS

Clinical findings	4 hours			one week		
	Levodopa-c	Vicia faba	P-Value	Levodopa-c	Vicia faba	P-Value
Rigidity	1.16	1.13	0.56	1.66	1.33	0.56
Tremor at rest	2.00	1.76	0.02	1.70	1.53	0.02
Rising chair	1.13	1.06	0.41	1.33	1.03	0.25
Gait	0.83	0.93	0.25	0.80	0.93	0.18
Freezing	0.80	0.63	0.02	0.76	0.63	0.04
Bradykinesia	1.06	1.00	0.41	1.06	1.00	0.41
Posture	1.00	0.96	0.31	1.00	0.96	31

The adverse drug reactions of nausea and vomiting were reported to occur significantly less frequently after 4 hours and one week with *faba* extract (p-value=0.012 and 0.004, respectively), and orthostatic hypotension was also reported to be significant (p-value=0.031). (Table 3)

Table-3: Adverse drug reaction and the comparison

Adverse reaction Number of sufferers (%)	4 hours			one week		
	Levodopa-c	Vicia faba	P-Value	Levodopa-c	Vicia faba	P-Value
Nausea	15 (50)	6 (20)	0.012	13 (43.3)	4 (13.3)	0.004
Orthostatic hypotension	8 (26.7)	2 (6.7)	0.031	7 (23.3)	2 (6.7)	0.063
Insomnia	-	-	-	7 (23.3)	6 (20)	1.000
Sleepiness	13 (43.3)	10 (33.3)	0.25	-	-	-
Loss of appetite	-	-	-	5 (16.7)	3 (10)	0.500

Docking analysis

A literature survey of the "Dictionary of Natural Product" database characterized fifty-one components, which are listed in Table 4.

The results of docking analysis, shown in Table 5, were given by docking score in kcal/mol. The following docking scores indicate the highest affinity of all evaluated ligands vs. each target: **VF-32** against 1H1D with a docking score value of -10.983 kcal/mol, **VF-27** against 1XQ8 with a docking score value of -4.9 kcal/mol, **VF-47** against 2BXR with a docking score value of -11.438 kcal/mol, **VF-43** against 2V5Z with a docking score value of -12.736 kcal/mol, and **VF-45** against 3UZA and 4I1H with docking score values of -11.428 and -10.974 kcal/mol, respectively. Both positive controls indicated moderate-weak affinity to the targets. The binding energies of l-DOPA (**VF-5**) against targets 1H1D, 1XQ8, 2BXR, 2V5Z, 3UZA, and 4I1H were obtained as -7.194, -2.905, -4.969, -8.51, -7.442, and -4.779 kcal/mol, respectively. Safinamide was also connected to the proteins with docking score values of -6.672 (vs. 1H1D), -1.086 (vs. 1XQ8), -4.733 (vs. 2BXR), -9.996 (vs. 2V5Z), -7.652 (vs. 3UZA), and -4.434 (vs. 4I1H) kcal/mol. A comparison of the results between l-DOPA as the major component of *faba* beans, and other metabolites of this plant confirmed a strong interaction for several compounds vs. targets, and they are probably responsible for the anti-Parkinson activity of the plant instead of dopamine.

Figure 1 shows the interactions of most active ligands with enzymes. The interactions study revealed that the major interactions between the active ligands and the enzymes were H-bond interactions of hydroxyl,

Table 4: Bioactive component of V. faba

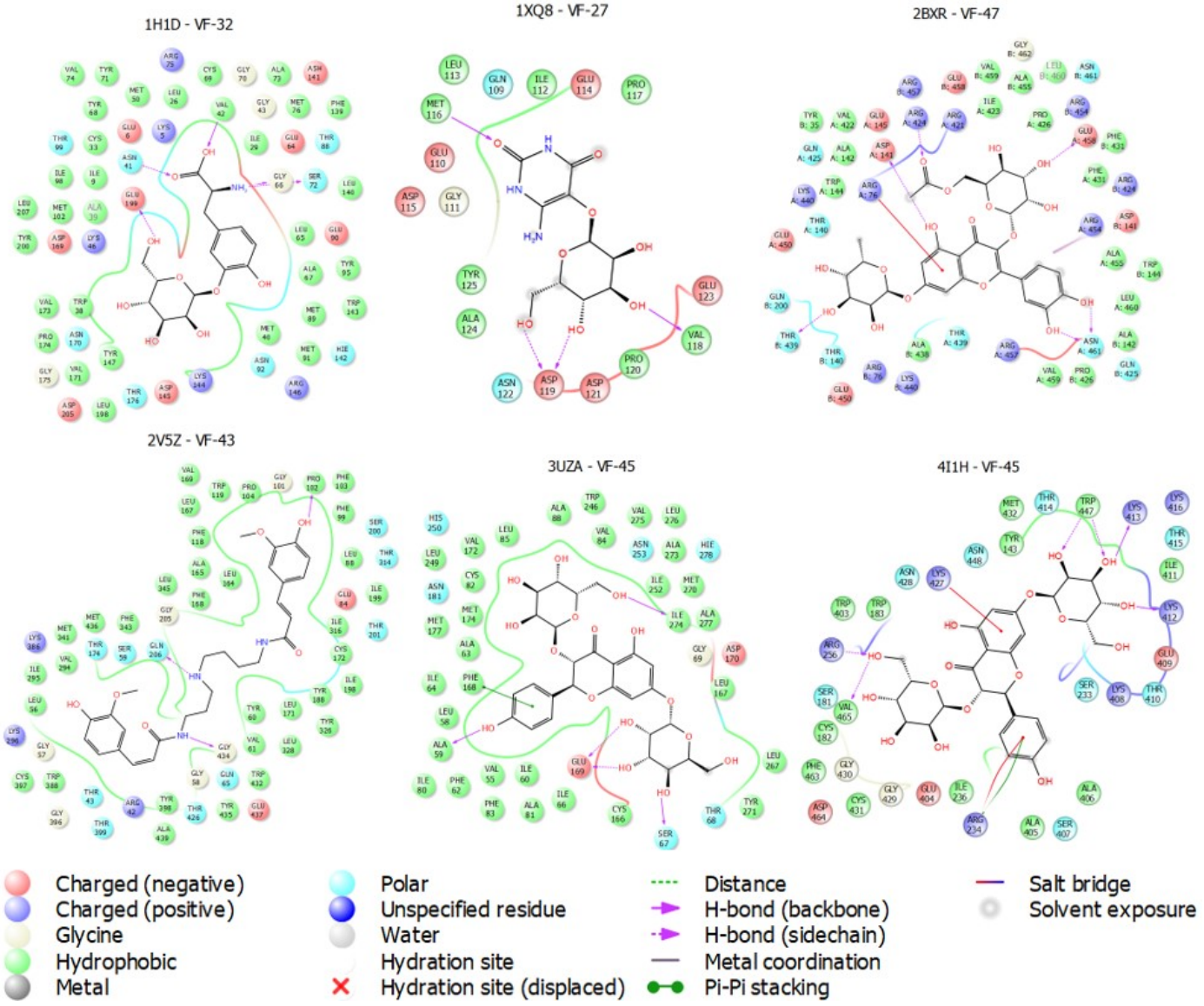
Label	Component Name	CAS registry number
VF-1	2,3-dihydroxy propanoic acid	6000-40-4
VF-2	methylene butanedioic acid	97-65-4
VF-3	epinine	501-15-5
VF-4	4-hydroxy citrulline	3618-90-4
VF-5	l-DOPA	59-92-7
VF-6	N^G,N^G-dimethyl arginine	30315-93-6
VF-7	N^G,N'^G-dimethyl arginine	30344-00-4
VF-8	7-didehydro jasmonic acid	120282-76-0
VF-9	N-carbamoyl	32507-69-0
VF-10	6,7-diepimer cucurbic acid	120330-52-1
VF-11	9,10-dihydro jasmonic acid	98674-52-3
VF-12	wyeronic acid	117783-52-5
VF-13	4-chlorotryptophan	52448-14-3
VF-14	(2E,11Z)-wyerone acid	54954-14-2
VF-15	2E,11Z)-11,12-dihydro wyerone acid	70711-57-8
VF-16	(2E,11Z)-wyerone acid methyl ester	20079-30-5
VF-17	(2E,11Z)-11,12-dihydro wyerone acid methyl ester	20450-54-8
VF-18	(2E,11Z)-8-hydroxy wyerone acid methyl ester	20450-52-6
VF-19	N^{γ}-glutamyl aspartic acid	16804-55-0
VF-20	(2E,11Z)-8-hydroxy-11,12-dihydro wyerone acid methyl ester	70711-58-9
VF-21	3α-hydroxy abscisic acid	84026-26-6
VF-22	(2E,11Z)-11,12-epoxide wyerone acid methyl ester	60375-16-8
VF-23	14-hydroxy abscisic acid	91897-25-5
VF-24	N-(4-hydroxy-E-cinnamoyl) 4-hydroxy phenethyl amine	36417-86-4
VF-25	N^2-(3-carboxy-2-hydroxy propanoyl) arginine	87605-92-3
VF-26	5-O-β-D-glucopyranoside-2,4-diamino-5,6-dihydroxy pyrimidine; two stereo isomers **a** & **b**	152-93-2
VF-27	5-O-β-D-glucopyranoside-4-amino-2,5,6-trihydroxy pyrimidine	19286-37-4
VF-28	N-jasmonoyl isoleucine	120330-93-0
VF-29	N-jasmonoyl dopamine	No found
VF-30	gibberellin A_{44}	36434-15-8
VF-31	gibberellin A_{53}	51576-08-0
VF-32	3'-O-β-D-glucopyranoside-2-amino-3-(3,4-dihydroxy phenyl) propanoic acid	2275-95-8
VF-33	N-jasmonoyl tyrosine	105801-18-1
VF-34	4''',4''''-dihydroxy-N,N'-dicinnamoyl putrescine	37946-59-1
VF-35	N-jasmonoyl-2-amino-3-(3,4-dihydroxy phenyl) propanoic acid	866421-54-7
VF-36	N-jasmonoyl tryptophan	113762-87-1
VF-37	7α-hydroxy-N-jasmonoyl tryptophan	113762-88-2
VF-38	N,N''-bis(4-hydroxy cinnamoyl) spermidine	65715-79-9
VF-39	3''',3''''-dimethoxy, 4''',4''''-dihydroxy-N,N'-dicinnamoyl putrescine	42369-86-8
VF-40	3,28-dihydroxy-20(29)-lupene	473-98-3
VF-41	brassinolide	78821-43-9
VF-42	N-[[3-(β-D-glucopyranosyloxy)-2,3-dihydro-2-oxo-1H-indol-3-yl]acetyl]aspartic acid	99694-85-6
VF-43	N,N''-bis(4-hydroxy-3-methoxy cinnamoyl) spermidine	70185-61-4
VF-44	3-O-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside kaempferol 3,7-diglycosides	38784-79-1
VF-45	3,7-di-O-β-D-glucopyranoside-3,4',5,7-tetrahydroxy flavanone	80212-10-8
VF-46	3-O-(6-O-acetyl-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside kaempferol 3,7-diglycosides	124097-45-6
VF-47	3-O-(6-O-acetyl-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside quercetin 3,7-diglycosides	124027-51-6
VF-48	3-O-[α-L-rhamnopyranosyl-(1→2)-β-D-galactopyranoside], 7-O-α-L-rhamnopyranoside kaempferol 3,7-diglycosides	124027-49-2
VF-49	3-O-[α-L-Rhamnopyranosyl-(1→2)-6-O-acetyl-β-D-galactopyranoside], 7-O-α-L-rhamnopyranoside Kaempferol 3,7-diglycosides	124027-50-5
VF-50	fabacyl acetate	No found

carbonyl, and amino groups as well as π-π stacking of the aromatic rings with the active site of the enzymes.

Table 5.Docking analysis of the chemical constituents of V. faba against six effective proteins in Parkinson's disease

compound	docking score (Kcal/mol)					
	1H1D	**1XQ8**	**2BXR**	**2V5Z**	**3UZA**	**4I1H**
VF-1	-5.208	-3.197	-4.08	-5.368	-4.697	-3.277
VF-2	-3.803	**-4.583**	-5.01	-5.762	-5.103	-3.593
VF-3	-6.502	-1.502	-4.111	-6.496	-7.585	-4.123
VF-4	-7.125	-3.583	-4.514	-6.454	-5.078	-5.468
VF-5; Levodopa	**-7.194**	**-2.905**	**-4.969**	**-8.51**	**-7.442**	**-4.779**
VF-6	-6.46	-1.368	-2.119	-3.655	-3.835	-2.278
VF-7	-7.083	-1.778	-3.951	-5.207	-5.134	-3.56
VF-8	-5.777	-1.364	-3.308	-7.934	-6.433	-3.969
VF-9	-5.641	-2.6	-3.935	-8.628	-7.353	-3.995
VF-10	-4.71	-0.912	-3.91	-8.181	-7.467	-5.268
VF-11	-5.169	-1.466	-3.413	-8.81	-8.033	-3.115
VF-12	-5.861	-0.602	-2.715	-8.445	-8.633	-3.588
VF-13	-4.808	-2.298	-4.573	-8.209	-7.846	-3.742
VF-14	-5.415	-0.272	-2.371	-7.882	-7.485	-2.618
VF-15	-6.715	-0.447	-2.871	-9.27	-8.08	-3.275
VF-16	-5.735	-0.153	-2.344	-8.928	-7.307	-1.742
VF-17	-4.753	-0.01	-2.643	-7.52	-6.907	-2.068
VF-18	-4.336	0.227	-3.121	-8.624	-7.852	-4.319
VF-19	-6.474	-3.905	-6.283	-8.438	-5.916	-4.511
VF-20	-4.218	0.042	-2.73	-7.824	-8.371	-3.85
VF-21	-3.785	-2.273	-3.371	-7.808	-7.121	-4.27
VF-22	-5.761	-0.437	-3.592	-8.97	-8.8	-2.902
VF-23	-5.274	-2.613	-4.641	-9.787	-7.927	-5.574
VF-24	-7.202	1.061	-2.833	-8.73	-8.529	-3.382
VF-25	-6.29	-3.393	-6.464	-8.469	-7.766	-6.025
VF-26-a	-5.343	-3.552	-5.877	-8.085	-5.912	-7.12
VF-26-b	-5.963	**-4.799**	-7.419	-9.056	-6.259	-6.812
VF-27	-5.397	**-4.9**	-5.869	-7.159	-7.599	-7.006
VF-28	-6.722	-1.216	-5.074	-10.13	-8.684	-4.12
VF-29	-7.576	-1.638	-4.64	-9.548	**-9.593**	-5.021
VF-30	-3.056		-3.965		-4.425	-4.059
VF-31	-4.052	-2.155	-3.794			-4.58
VF-32	**-10.983**	-3.03	-7.757	-10.983	**-9.39**	-7.719
VF-33	-5.806	-1.739	-7.228	-8.975	-8.245	-4.876
VF-34	**-8.057**	-0.805	-6.06	-10.661	-8.037	-4.185
VF-35	-2.869	-2.096	-5.381	-10.453	-8.508	-5.647
VF-36	-2.948	-0.969	-5.595	**-11.019**	**-9.874**	-3.923
VF-37	-6.852	-2.234	-5.56	**-11.676**	**-9.57**	-4.647
VF-38	-7.564	-0.776	-7.015	**-12.279**	-8.69	-4.814
VF-39	**-8.605**	-0.16	-6.018	**-11.677**	-8.227	-5.26
VF-40		-0.359	-3.544			-1.853
VF-41	-2.456	-0.984	-6.439		-4.121	-5.163
VF-42	-5.976	**-4.253**	-8.46	-10.811	-9.185	-6.888
VF-43	**-8.891**	-0.253	-7.108	**-12.736**	-8.525	-5.956
VF-44	-6.09	-3.294	**-9.483**		-9.048	**-9.108**
VF-45	-7.481	-3.827	**-9.412**		**-11.428**	**-10.974**
VF-46	-7.373	-3.01	**-9.422**		-7.626	-8.258
VF-47	-5.522	-3.935	**-11.438**		-9.117	**-9.244**
VF-48	-6.649	**-4.599**	**-10.318**		**-9.66**	**-9.963**
VF-49	-5.696	**-4.225**	**-10.915**		-6.594	**-10.491**
VF-50	-3.394	-1.828	-3.114		-4.231	-3.424
Safinamide	**-6.672**	**-1.086**	**-4.733**	**-9.996**	**-7.652**	**-4.434**

Figure 1: The interactions of most active ligands with enzymes



Discussion

In this trial, the effect of 25 milliliter of *V. faba* extract that contains 106.5 mg of levodopa mixed with carbidopa was evident.

It can be concluded that fava bean may be a safe and effective alternative for levodopa-C. Moreover, because of its high amounts of vitamins and minerals, it may even have a disease-modifying effect, but this requires further investigations. During the trial period *V. faba* extract had substantial lower serum dopamine levels, but in most of the end points it had the same efficacy. These observations are consistent with small previous pilot studies[2,6]. Despite the higher overall levodopa serum level in the conventional treatment group, the fava bean extract could significantly alleviate all studied end points in this trial; however, conventional treatment had a significantly better effect on patient symptoms of tremor at rest and freezing.

It is of great importance to address whether these outcomes can be confirmed and whether benefits seen at 7 days will endure and translate into long-term benefits in clinically significant areas such as impairment of gait and balance.

COMT is an enzyme that metabolizes levodopa in the bloodstream. By blocking COMT, levodopa can penetrate further into the brain, thereby increasing the effectiveness of treatment, which is responsible for the recognition and degradation of damaged proteins found to be impaired in cases of PD [12]. Levodopa or its agonists can be prescribed to treat Parkinson's disease to compensate the dopamine depletion. The inhibitors of the aforementioned enzymes can be additionally applied to block dopamine degradation and control dopamine levels. Apart from levodopa which is one of the major components of fava bean, there are several other compounds in the plant that, based on the results of docking analyses, some of them could successfully connect to the active site of enzymes. Therefore, the anti-Parkinsonian effect of fava bean extract can be justified based on the combination of levodopa and several strong enzyme inhibitors (mentioned above).

Conclusion

This study showed the beneficial effect of *Vicia faba L.* similar to levodopa-C. From a practical point of view, the study results suggest a possible benefit of fava bean extract because of better compliance due to lower adverse events.

Study limitation and strength

There was no restriction in dietary intake of tyramine, and certain antidepressant agents were allowed. A zero dropout rate during the study should be considered as an important strength of this study.

Conflict of interest

There are no known conflicts of interest associated with this publication.

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm*. 2017;124(8):901-905. doi:10.1007/s00702-017-1686-y
2. Rabey JM, Vered Y, Shabtai H, Graff E, Harsat A, Korczyn AD. Broad bean (Vicia faba) consumption and Parkinson's disease. *Adv Neurol*. 1993;60:681-684.
3. Ramírez-Moreno JM, Salguero Bodes I, Romaskevych O, Duran-Herrera MC. Broad bean (Vicia faba) consumption and Parkinson's disease: a natural source of L-dopa to consider. *Neurol Barc Spain*. 2015;30(6):375-376. doi:10.1016/j.nrl.2013.08.006
4. Salehi B, Abu-Reidah IM, Sharopov F, et al. *Vicia plan* ts—A comprehensive review on chemical composition and phytopharmacology. *Phytother Res*. 2021;35(2):790-809. doi:10.1002/ptr.6863
5. Roohani M, Ali Shahidi G, Miri S. Demographic study of parkinson's disease in Iran: Data on 1656 cases. *Iran J Neurol*. 2011;10(1-2):19-21.
6. Apaydin H, Ertan S, Ozekmekçi S. Broad bean (Vicia faba)--a natural source of L-dopa--prolongs "on" periods in patients with Parkinson's disease who have "on-off" fluctuations. *Mov Disord Off J Mov Disord Soc*. 2000;15(1):164-166. doi:10.1002/1531-8257(200001)15:1<164::aid-mds1028>3.0.co;2-e
7. Malathi R, Prashanthi K, Karthikeyan J. Molecular docking of fisetin as a multi-target drug in the treatment of Parkinson's disease. *J Drug Deliv Ther*. 2019;9(1-s):1-4. doi:10.22270/jddt.v9i1-s.2232
8. Obeso JA, Stamelou M, Goetz CG, et al. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy: The Shaking Palsy: Past, Present and Future. *Mov Disord*. 2017;32(9):1264-1310. doi:10.1002/mds.27115
9. Bujji babu N, Srinivasa rao P, Ramesh raju R. development of new robust rp hplc method for analysis of levo dopa in formulations. *Int J Sci Invent Today IJSIT*. 2012;1(2):130-144.
10. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord Off J Mov Disord Soc*. 2008;23(15):2129-2170. doi:10.1002/mds.22340
11. Vasavi HS, Sudeep HV, Lingaraju HB, Shyam Prasad K. Bioavailability-enhanced Resveramax™ modulates quorum sensing and inhibits biofilm formation in Pseudomonas aeruginosa PAO1. *Microb Pathog*. 2017;104:64-71. doi:10.1016/j.micpath.2017.01.015
12. Monteiro AFM, Viana JDO, Nayarisseri A, et al. Computational Studies Applied to Flavonoids against Alzheimer's and Parkinson's Diseases. *Oxid Med Cell Longev*. 2018;2018:1-21. doi:10.1155/2018/7912765

*****