PREDICTION OF ANTI-PARKINSON POTENTIAL OF PHYTOCONSTITUENTS USING PREDICTION OF ACTIVITY SPECTRA OF SUBSTANCES SOFTWARE

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ABSTRACT

Objective: Neurodegenerative disorders are group of diseased conditions in which there is loss of neuron cells occur. The main objective of this study to find/search out the phytochemical with the help of prediction of activity spectra of substances (PASS), those show maximum activity over the selected targets of the Parkinson's disease (PD).

Methods: PASS is a valuable software which is used in this study, to predict the anti-Parkinson activity of different compounds. Canonical simplified molecular-input line-entry system is used for the prediction of anti-Parkinson activity which is obtained from PubChem website. The predicted activity also compared with marketed compound like levodopa.

Results: From the study, it was found that resveratrol was the only compound which has the activity on all the selected targets. On the other hand, stemazole and celastrol were found to have the least active compounds as both have the activity only on a single target.

Conclusion: In this research work, we tried to compile the information regarding the PASS predicted anti-Parkinson activity of some important phytoconstituents. We found that resveratrol can be a target for further investigation in the development of drug therapy for PD.

Keywords: Parkinson's disease, Prediction of activity spectra of substances, Levodopa, Postural instability.

INTRODUCTION

Parkinson disease (PD) is the second most common, age-related chronic neurodegenerative disorder. Nowadays, PD is the most prevalent disease. Approximate 7–10 million people of the world surviving with the PD, of these 1 million lives in the U.S. men are at a greater risk of PD compared to woman. As the age increases, the incidence of PD also increases. Mostly the people with the age of 60 years or above are the targets of the PD. PD becomes the 14th leading cause of death in the U.S [1,2]. The key symptoms of PD are tremors, rigidity, bradykinesia, postural instability, cognitive dysfunction, and sleep disturbance. These symptoms appeared due to progressive loss of dopaminergic neurons in substantia nigra pars compacta of brain, which further lead to loss of dopamine (DA) [2,3]. Another pathological hallmark of PD is the presence of eosinophilic intracytoplasmic proteinaceous inclusion bodies that are mainly composed of fibrillar α-synuclein termed Lewy bodies and dystrophic neurites (Lewy neurites) presents in surviving neurons [4].

The etiology of PD is still unknown, but there are several factors such as environmental, genetics, age, and medication which can be responsible for the development of PD. The available drug therapy which includes levodopa and carbidopa provide only symptomatic relief but able to cure the underline cause of the PD. These drugs also produce certain side effects such as nausea, vomiting, hallucination, convulsions, and dry mouth (Fig. 1) [1,5].

Herbal medicines have a long history of safe and efficacious administration as therapeutic agent or dietary supplement in different parts of the world. Due to the presence of various type of phytochemical in them, these herb possesses protective and therapeutic effect in various indications. Nowadays, plant chemicals are of great interest for the development of medicine for various diseases [6]. Development of new safe and effective medicine is not an easy task. Various phytochemicals have been reported to be effective in *in vitro* and *in vivo* models of PD, but no one can enter into the mainstream of drug development due to lack of information.

Prediction of activity spectra for substances (PASS) is a computer-based software, which provides the information regarding the biological activities on different targets of the chemical compound on the bases of their chemical structure. The software predicts the activity of the compound in two probabilities; one is probable activity (Pa) and another one is probable inactivity (Pi). The value of Pa and Pi varies from 0.000 to 1.000. If Pa > Pi for any activity, only then that activity can be designated to the compound. If Pa value is more than 0.7 for any activity, then the probability of that action is high in pharmacological experiment. If Pa value is more than 0.5 but <0.7 for any activity, then the probability of that action is less in pharmacological experiment. If Pa value is <0.5, then the probability of observing that activity in pharmacological experiment is less [7-10].

METHODS

For the evaluation of the activity using PASS, first, we select certain phytoconstituents which have already reported to have pharmacological effect in the *in vivo* and *in vitro* models of PD, and one marketed standard drug compound for PD that is levodopa. For the prediction of activity in the different targets of PD, canonical simplified molecular-input line-entry system (SMILES) is used which is obtained from PubChem website shown in Table 1. These SMILES work as a molecular formula of the compound and are directly copied into the PASS software to predict the activity.

RESULTS

The selected phytochemical and marketed compound was predicted using PASS for nine activities in the PD shown in Table 2. These activities are as follows:
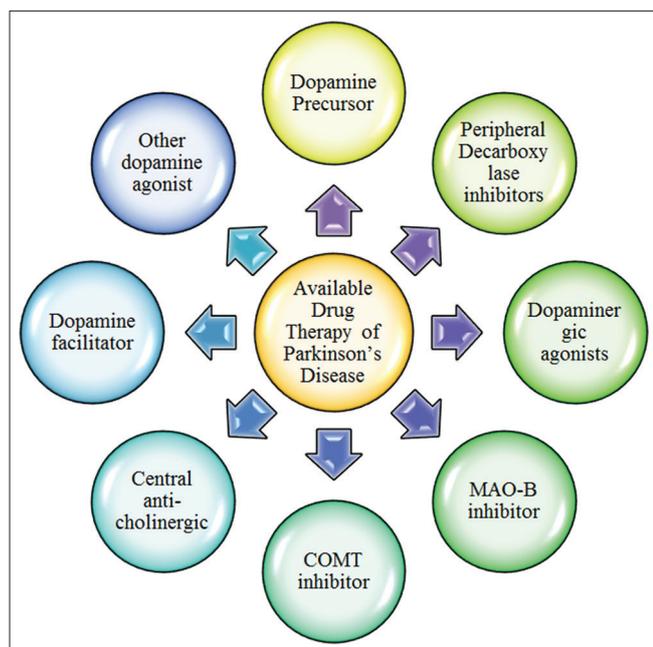
Fig. 1: Available drug therapy of Parkinson disease

- DA precursor
- Caspase 3 inhibitor
- Anticholinergic
- Free radical scavenger
- Nootropic activity
- Monoamine oxidase (MAO) inhibitor
- DA release stimulant
- N-methyl D-aspartate (NMDA) receptor antagonists
- Antiparkinsonian.

The predicted Pa predicted by PASS is represented in Table 2 and also compared with the marketed drug that is levodopa.

DISCUSSION

PD is a progressive neurodegenerative disorder, for which till now an effective treatment is not available. Research is going on overall the world in this stream. Several compounds have passes the preclinical trails but able to come into the clinical trial phase, due to lack of informative data. PASS is online software, which can be used by anyone after completing free registration. This software predicts the biological activity of the chemical compound on the bases of chemical structure and interaction with the different targets. This software provides an information regarding that a particular compound can be beneficial in a particular disease. On the basis of which further pharmacological

Table 1: Phytochemicals with canonical SMILES and chemical structure

Name of compound	Canonical SMILES	Chemical structure
Levodopa	C1=CC(=C (C=C1CC (C(=O) O) N) O) O	
Nicotine	CN1CCCC1C2=CN=CC=C2	
Caffeine	CN1C=NC2=C1C(=O) N (C(=O) N2C) C	
Resveratrol	C1=CC(=CC=C1C=CC2=CC(=CC(=C2) O) O) O	
Riluzole	C1=CC2=C (C=C1OC (F)(F) F) SC(=N2) N	

(Contd...)

Table 1: (*Continued*)

Name of compound	Canonical SMILES	Chemical structure
Hesperidin	CC1C (C (C (C (O1) OCC2C (C (C (C (O2) OC3=CC(=C4C(=O) CC (OC4=C3) C5=CC(=C (C=C5) OC) O) O) O) O) O) O) O) O	
Baicalein	C1=CC=C (C=C1) C2=CC(=O) C3=C (C(=C (C=C3O2) O) O) O	
Acetylcholine	CC(=O) OC1CC2=CC3=C (C=C2C4C1(C5=C (CN4C) C6=C (C=C5) OCO6) C) OCO3	
n-Butylidenephthalide	CCCC=C1C2=CC=CC=C2C(=O) O1	
Stemazole	C1=CC(=CC=C1C2=NNC(=S) O2) NC(=S) NN	
Celastrol	CC1=C (C(=O) C=C2C1=CC=C3C2(CCC4(C3(CCC5(C4CC (CC5)(C) C(=O) O) C) C) C) C) O	
L-theanine	CCNC(=O) CCC (C(=O) O) N	
Kaempferol	C1=CC(=CC=C1C2=C (C(=O) C3=C (C=C (C=C3O2) O) O) O) O	
Carnosic acid	CC (C) C1=C (C(=C2C(=C1) CCC3C2(CCCC3(C) C) C(=O) O) O) O	
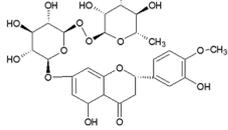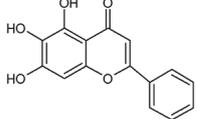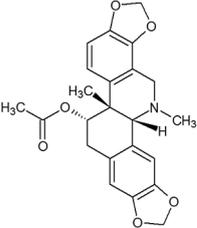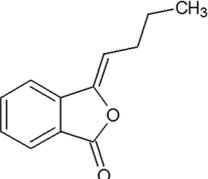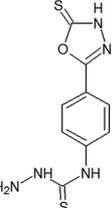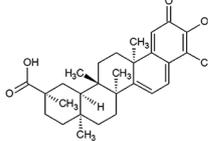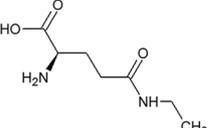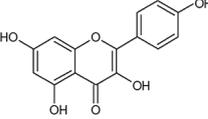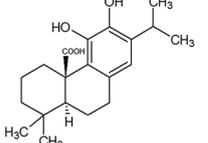
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Table 1: (*Continued*)

Name of compound	Canonical SMILES	Chemical structure
Gastrodin	C1=CC(=CC=C1CO) OC2C (C (C (C (O2) CO) O) O) O	
Trehalose	C (C1C (C (C (C (O1) OC2C (C (C (C (O2) CO) O) O) O) O) O) O) O	
Rosmarinic acid	C1=CC(=C (C=C1CC (C(=O) O) OC(=O) C=CC2=CC(=C (C=C2) O) O) O) O	
Shogaol	CCCCCC=CC(=O) CCC1=CC(=C (C=C1) O) OC	
Zingerone	CC(=O) CCC1=CC(=C (C=C1) O) OC	
Syringic acid	COC1=CC(=CC(=C1O) OC) C(=O) O	
Fisetin	C1=CC(=C (C=C1C2=C (C(=O) C3=C (O2) C=C (C=C3) O) O) O) O	
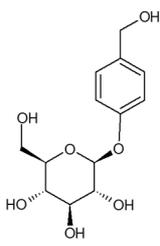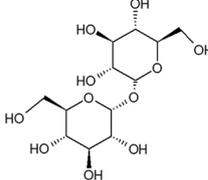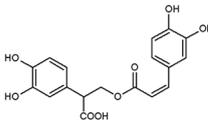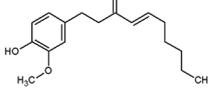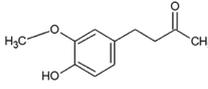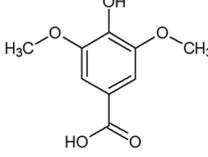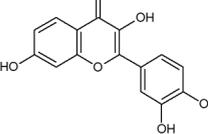
SMILES: Simplified molecular-input line-entry system

testing can be performed to verify the result or the pre-performed pharmacological testing can get support from the information provided by the software.

In this study, we select certain phytoconstituents which have been reported to have beneficial effects in the *in vivo* and *in vitro* models of PD. One marketed standard drug (levodopa) for PD is also selected to compare with the phytoconstituents. All compounds were tested for nine activities as shown in Fig. 2. We found that levodopa has the highest DA precursor activity when compared to the selected phytoconstituents (Fig. 3). Of the phytoconstituents, rosmarinic acid has the higher value for DA precursor activity and fisetin has the lowest one.

The phytoconstituents which show DA precursor activity follow the pattern rosmarinic acid > trehalose > zingerone > L-theanine, resveratrol > gastrodin > syringic acid > shogaol > fisetin.

Levodopa was found to have least caspase 3 inhibitory activity, and only four phytochemicals show caspase 3 inhibitory activity, Fig. 4. L-theanine has the highest value and resveratrol has the least but more than levodopa. The value varies such as l-theanine > syringic acid > n-butylidenephthalide > resveratrol > levodopa. Similarly, only three phytochemicals show anticholinergic activity nicotine > acetylcholine > resveratrol, and same was absent in case of levodopa.

In case of anticholinergic activity, only three compounds were found to have the anticholinergic activity shown in Fig. 5. Nicotine has the highest activity followed by acetylcholine and resveratrol, respectively.

Hesperidin was found to have the highest free radical scavenging activity shown in Fig. 6. Levodopa also found to have free radical scavenging activity, but most of the phytochemicals were found to have more value for the same activity, Hesperidin > kaempferol > fisetin >

Table 2: Pa predicted by PASS software

Name of compound	Pa predicted by the PASS software									
	Reported activity	DA precursor	Caspase 3 inhibitor	Anticholinergic	Free radical scavenger	Nootropic activity	MAO inhibitor	DA release stimulant	NMDA receptor antagonists	Antiparkinsonian
Levodopa	DA agonist [11]	0.618	0.113	NP	0.377	0.371	0.123	0.547	0.186	0.375
Nicotine	Increase DAT level [12]	NP	NP	0.718	NP	0.879	NP	0.213	0.026	0.512
Caffeine	Decreases level of ROS, and increase the level of SOD and GHS [13]	NP	NP	NP	NP	0.69	0.118	NP	NP	0.521
Resveratrol	Decreases ROS conc., and apoptosis [14]	0.058	0.151	0.117	0.577	0.423	0.294	0.446	0.232	0.329
Riluzole	Decrease the depletion striatal DA and DOPAC [15]	NP	NP	NP	0.163	NP	0.122	0.205	NP	0.590
Hesperidin	Improve memory impairment, decreases level of ROS, improve activity of CAT and GPx, and level of DA [16]	NP	NP	NP	0.991	NP	0.092	NP	NP	NP
Baicalein	Decreases TH positive neurons and astrocyte activation [17]	NP	NP	NP	0.705	0.424	0.359	0.486	0.124	0.241
Acetylcholine	Decreases DA neuron loss, and alpha-synuclein aggregation [18]	NP	NP	0.22	NP	0.351	NP	NP	NP	0.242
n-Butylidenephthalide	Decreases aggregation of alpha-synuclein, DA depletion [19]	NP	0.156	NP	0.259	NP	0.062	0.212	0.102	0.285
Stemazole	Improve muscle coordination, decrease level of ROS, and increase activity of SOD, GSH, and level of DAT [20]	NP	NP	NP	NP	NP	0.372	NP	NP	NP
Celastrol	Decreases dopaminergic neuron loss, TNF alpha, DA depletion [21]	NP	NP	NP	NP	0.755	NP	NP	NP	NP
L-theanine	Decreases caspase 3 activity [22]	0.058	0.180	NP	0.293	0.576	NP	0.300	0.195	0.278
Kaempferol	Decreases dopaminergic neuron loss, increases SOD and GPx activity [23]	NP	NP	NP	0.774	0.348	0.538	0.217	0.113	NP
Carnosic acid	Decreases lipid peroxidation and caspase 3 activity [24]	NP	NP	NP	0.482	NP	NP	NP	NP	0.284
Gastrodin	Decreases caspase 3 activity [25]	0.057	NP	NP	0.739	NP	NP	NP	NP	NP
Trehalose	Decreases DA, HVA depletion, and glial activation [26]	0.060	NP	NP	0.627	NP	NP	NP	0.095	NP
Rosmarinic acid	Decreases apoptosis, restoration of complex 1 activity and decreases level of ROS [27]	0.080	NP	NP	0.745	NP	NP	0.286	0.099	NP
Shogaol	Decreases dopaminergic neuron loss and glial cell activation [28]	0.044	NP	NP	0.743	0.411	NP	0.358	0.097	NP
Zingerone	Decreases free radical conc., and DA depletion [29]	0.059	NP	NP	0.695	0.603	0.106	0.532	0.132	0.213
Syringic acid	Decreases DA depletion, lipid peroxidation, increases level of GSH, DAT [30]	0.047	0.178	NP	0.628	0.389	NP	0.431	0.128	0.285
Fisetin	Decreases alpha-synuclein expression and level of inflammatory mediator [31]	0.031	NP	NP	0.753	NP	NP	0.258	NP	NP

NP: Not predicted, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxide, GSH: Glutathione, DA: Dopamine, DOPAC: Dihydroxyphenylacetic acid, DAT: Dopamine transporter; TNF-α: Tumour necrosis factor-α, ROS: Reactive oxygen species, HVA: Homovanillic acid, PASS: Prediction of activity spectra of substances, Pa: Probable activity, MAO: Monoamine oxidase, NMDA: N-methyl D-aspartate, GHS: Growth hormone secretagogue
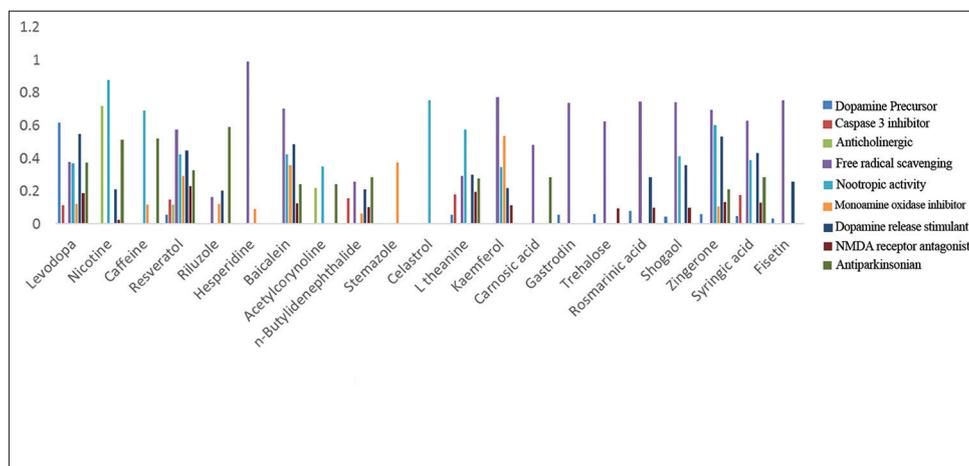
**Fig. 2: All activities of all compounds with respect to levodopa**
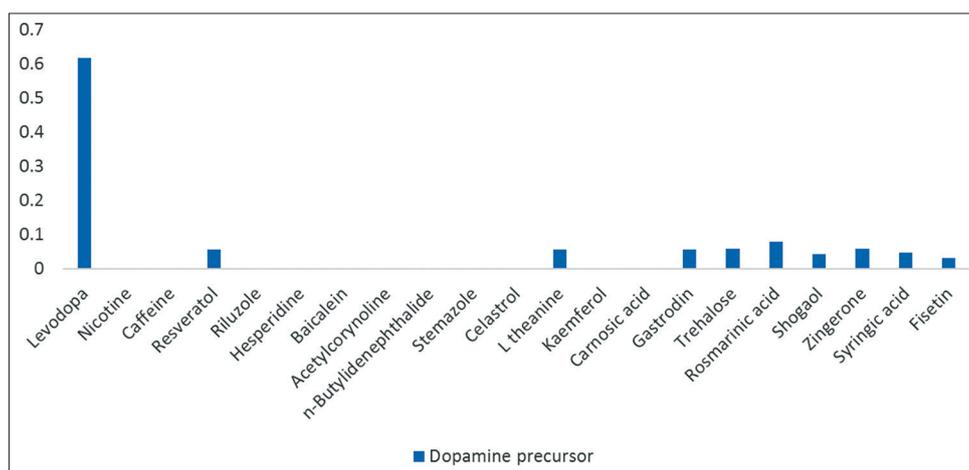
Fig. 3: Dopamine precursor activity of all compounds with respect to levodopa
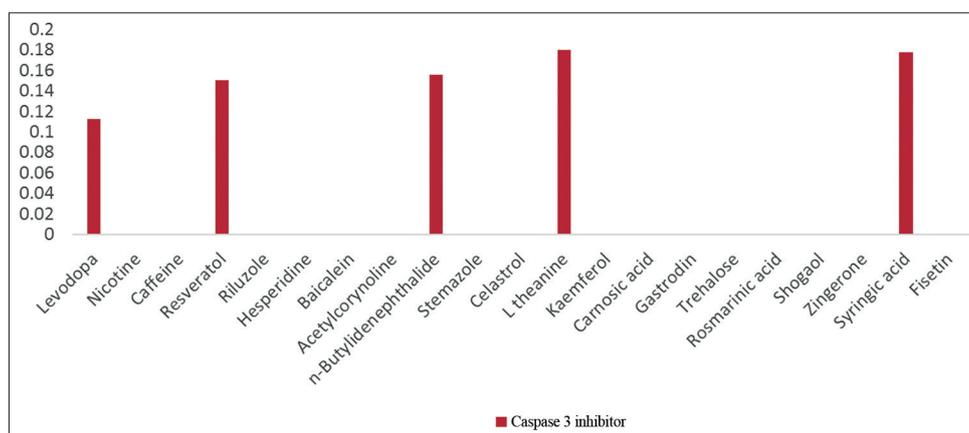

Fig. 4: Caspase 3 inhibitor activity of all compounds with respect to levodopa

rosmarinic acid > shogaol > gastrodin > baicalein > zingerone > syringic acid > trehalose > resveratrol > carnosic acid > levodopa > l-theanine > n-butylidenephthalide > riluzole. Rosmarinic acid and shogaol have value almost near to each other.

Again in case of nootropic activity, most of the phytochemicals have the higher value than the levodopa, and according to value list is like: Nicotine > celastrol > caffeine > zingerone > l-theanine > baicalein > resveratrol > shogaol > syringic acid > levodopa >

acetylcholine > kaempferol. Resveratrol, baicalein, kaempferol, and acetylcholine have activity values near to each other shown in Fig. 7.

In MAO inhibiting activity, kaempferol has the highest value than another phytochemicals and also more than levodopa, kaempferol > stemazole > baicalein > resveratrol > levodopa > riluzole > caffeine > zingerone > hesperidin > n-butylidenephthalide as shown in Fig. 8.
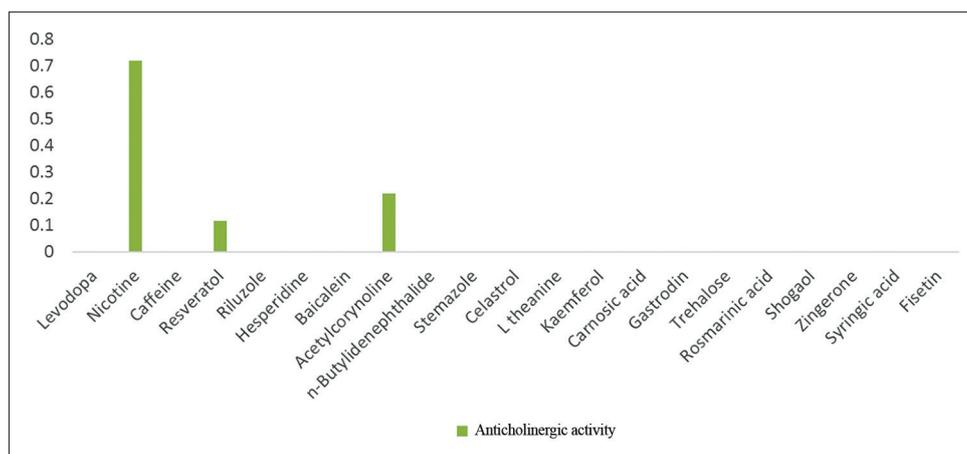
**Fig. 5: Anticholinergic activity of all compounds with respect to levodopa**
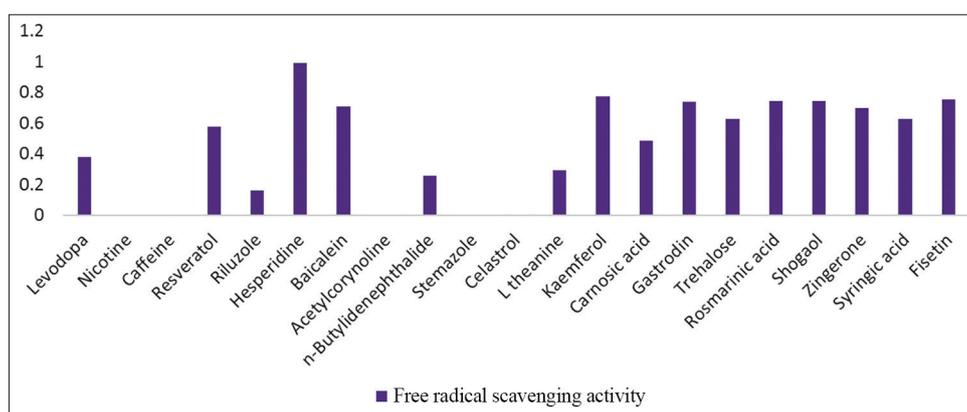
**Fig. 6: Free radical scavenging activity of all compounds with respect to levodopa**
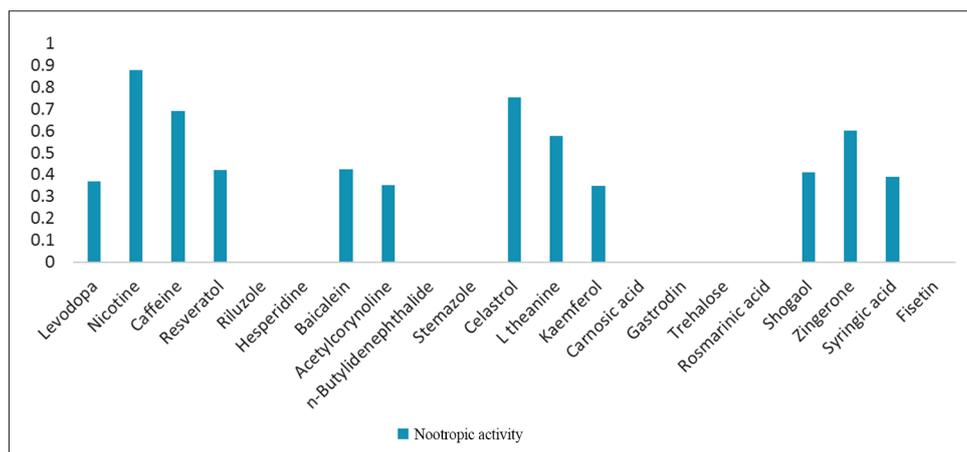
Fig. 7: Nootropic activity of all compounds with respect to levodopa

Levodopa was found to have the highest DA release stimulant activity, when compared to the selected phytochemicals shown in Fig. 9. Zingerone found to have the highest value among the phytochemicals but less than levodopa. Other compounds having DA release activity are as follow: Levodopa > zingerone > baicalein > resveratrol > syringic acid > shogaol > l-theanine > rosmarinic acid > fisetin > kaempferol > nicotine > n-butylidenephthalide > riluzole. Nicotine, kaempferol, and n-butylidenephthalide have to value almost near to each other.

In case of NMDA receptor antagonist activity, the phytochemicals does not have a good value even levodopa shown in Fig. 10. Resveratrol has the

highest value, but it is only 0.232 which is not much more than levodopa (0.186). The compound which shows the NMDA receptor antagonist activity, their values lie almost in the same range or slightly differ from each other.

Only two compounds resveratrol and l-theanine have more values than levodopa rest are having less than levodopa. Other compounds having NMDA receptor antagonist activity are as follow: Resveratrol > l-theanine > levodopa > zingerone > syringic acid > baicalein > kaempferol > n-butylidenephthalide > rosmarinic acid > shogaol > trehalose > nicotine.
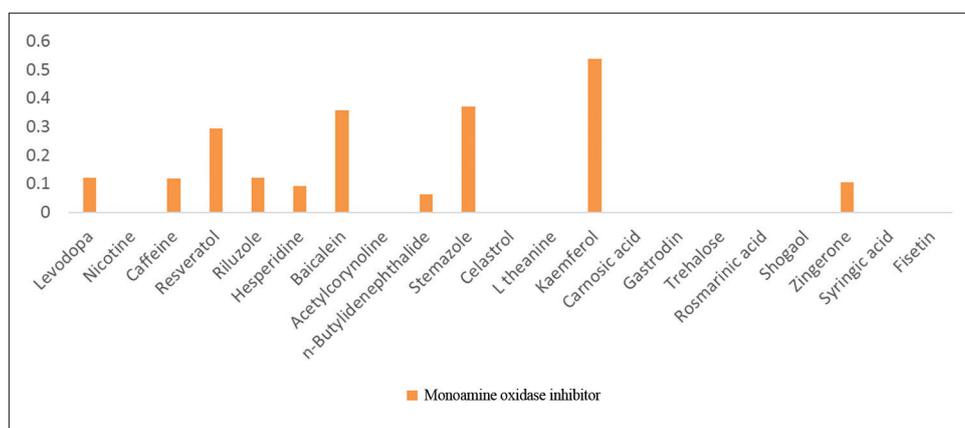
**Fig. 8: Monoamine oxidase inhibiting activity of all compounds with respect to levodopa**
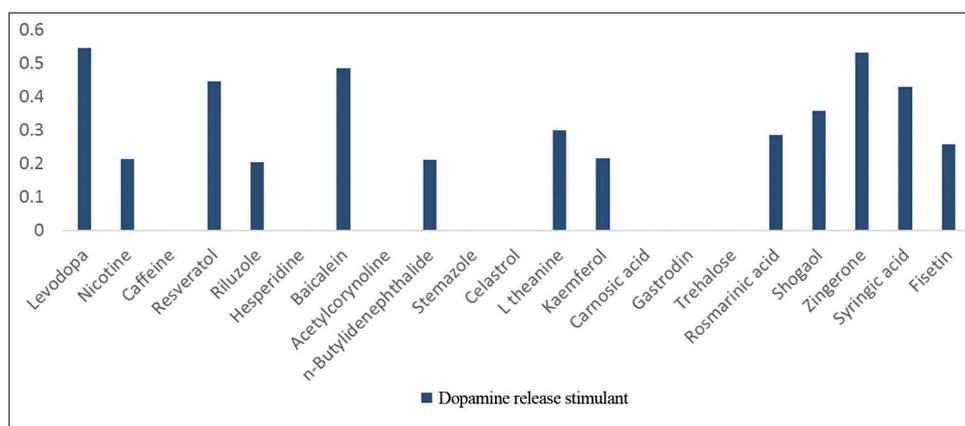
Fig. 9: Dopamine release stimulant activity of all compounds with respect to levodopa
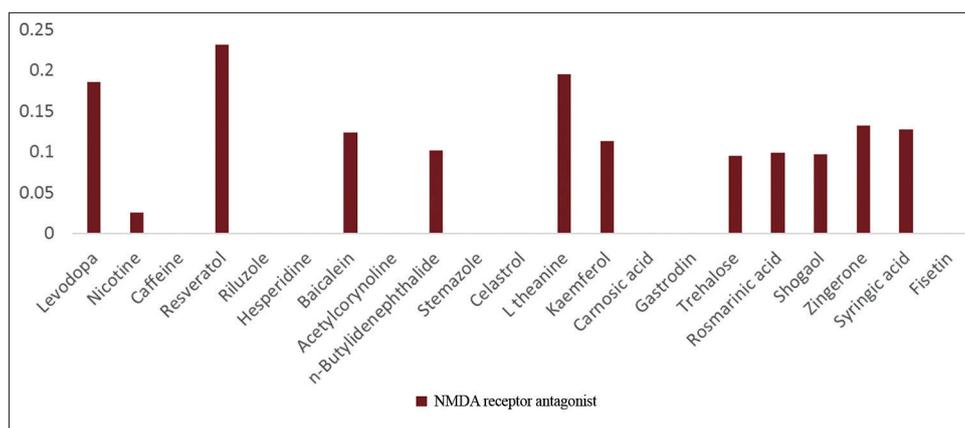

Fig. 10: N-methyl D-aspartate receptor antagonist activity of all the compounds with respect to levodopa

Being a standard drug therapy for PD, levodopa does not found to have a good antiparkinsonian activity, when compared to certain phytochemicals as shown in Fig. 11. Riluzole was found to have the highest antiparkinsonian activity among the phytochemicals and also more than levodopa. Carnosic acid, l-theanine, syringic acid, and n-butylidenephthalide have values near to each other, but syringic acid and n-butylidenephthalide have the same activity values.

Various phytochemicals are present in plants, but only few were explored for their pharmacological activities and rest are unexplored. Testing every compound by hit and trial method for pharmacological activity is not an easy task as it is tedious and costly. However, with the help of PASS, a pathway can be generated to evaluate the phytochemical for a particular pharmacological activity. PASS not only provides a supportive information for the pre-explored phytochemicals but also provides information regarding their hidden potential activities which previously not known.

CONCLUSION

From the above study, it can be concluded that PASS provides an informative data to support the reported activities of the phytochemicals. It can also help the researcher to decide and to prepare a protocol for
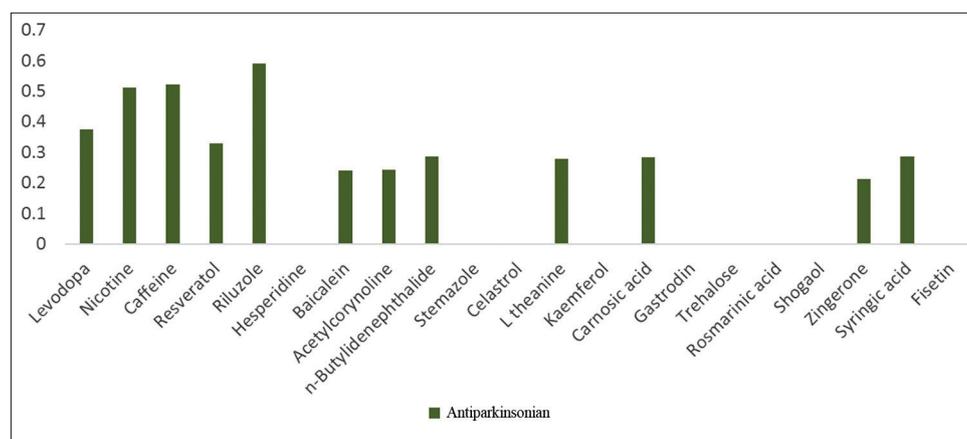
Fig. 11: Antiparkinsonian activity of all compounds with respect to the levodopa

testing a new phytochemical for a particular pharmacological action as well as to test a pre-reported phytochemical for a new activity.

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