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ORIGINAL ARTICLE **OPEN ACCESS**

In Silico Evaluation of Some Phenolic Acids for Their Neuroprotective Effect

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ABSTRACT

*Computational (**in silico**) methods are widely applied to pharmacology hypothesis development and testing. Different approaches are used to screen chemical structure of molecules and predict its possible biological targets. Phenolic acids are secondary plant metabolites with variety of beneficial pharmacological activities including neuroprotection. In this study, we have used different softwares i.e. Passonline, SwissADME and Protox II to predict biological activity, pharmacological effects, mechanism of action and toxicity of syringic acid and sinapic acid. This data is compared with standard neuroprotective drugs gabapentin and pregabalin. We found these phenolic acids could be neuroprotective as efficacious as used standard drugs. Syringic acid and sinapic acid can used clinically for various neuroprotective actions after passing through drug development process.*

***Keywords**: Gabapentin, Pregabalin, Protox II, Synapic acid, Syringic acid, SwissADME.*

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INTRODUCTION

The development of new highly effective and safe drugs is one of the most important and urgent tasks of modern pharmaceutical science. The inability of an investigational molecule to enter the pharmaceutical market is usually associated with safety and efficacy issues. Challenge is with physicochemical properties i.e. absorption, distribution, metabolism, excretion (ADME) and adverse effects of these new drugs. Assessment of ADME or toxic properties of new drugs using advanced techniques is time-consuming, exhaustive and expensive. Preclinical studies are not justified from ethical and economic point of view. Computational (*in silico*) studies are the rationale solution to these problems.[1] Using *in silico* experiments at the initial stages of drug development makes it possible to screen out most of the candidate compounds with unfavorable properties even before the start of in vivo and in vitro tests. This can significantly reduce financial investments, time, and labor costs, and also saves the lives of millions of laboratory animals.[1] Here in current study, various web based *in silico* methods like PASS bioactivity tester, SWISS ADME calculator and Protox II toxicity tester are used to explore the biological activities, efficacy and toxicity of syringic acid and sinapic acid. These are phenolic acids available in various fruits, cereals. Nuts and berries.[2] Availability of potent and safe drugs to treat CNS disorders is challenging as many synthetic drugs are associated with various adverse effects. Therefore, safe and potent natural products, which are active on brain, are targeted and used in treatment of psychiatric disorders viz. depression, anxiety, psychosis and neurodegenerative disorders.[3] So the current work was undertaken to predict biological activity, pharmacological effects, mechanism of action and toxicity of syringic acid and sinapic acid.

MATERIAL AND METHODS

1. PASS (Prediction of Activity Spectra for Substances): This software is used to evaluate drug likeness of molecule by exploring the general biological potential of an organic drug-like molecule. Various biological activities are predicted by his software depending on chemical structure of organic compounds. Virtual

molecules are screened before chemical synthesis and biological testing. Average accuracy of prediction estimated in leave-one-out cross-validation procedure for the whole PASS training set is about 96%. [4]

2. SwissADME: This software is developed by Swiss Institute of Bioinformatics. [5] Using this software, physicochemical, pharmacokinetic (ADME) and drug likeness properties of new molecules can be predicted which helps further in drug discovery and development process.

3. PROTOX II: It is a virtual lab used to predict toxicities of new molecules. The prediction of compound toxicities is an important part of the drug design development process. Prediction of toxicity using computational methods is faster method than preclinical experimentation. It also reduces the number of animal experiments. I his software different 33 models are used to predict different toxicities e.g. acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes pathways and toxicity targets.[6]

With the help of above softwares following evaluation done for syringic acid, sinapic acid, gabapentin and pregabalin.

1. Pharmacokinetic study: By using Passoline and SwissADME
2. Pharmacological study: By using Passoline
3. Prediction of possible target proteins: By using Passoline and SwissADME
4. Toxicity study: By using Passoline and Protox II

RESULTS AND DISCUSSION

Table 1: Pharmacokinetic parameters of Syrigic acid, Sinapic acid, Gabapentin and Pregabalin using Passoline and SwissADME

Sr. No.	Parameter	Test Drug		Standard Drug	
		Sinapic acid	**Syringic acid**	**Gabapentin**	**Pregabalin**
1.	Formula	C11H12O5	C9H10O5	C8H15NO2	C8H17NO2
2.	M.W.	224.21	198.17	157.21	159.23
3.	H-BondAcceptors	5	5	3	3
4.	H-bond donors	2	2	2	2
5.	Rotatable bonds	3	4	2	5
6.	TPSA	75.99	75.99	63.32	63.32
7.	iLOGP	1.63	1.54	0.85	1.06
8.	WLOGP	1.4	1.11	1.12	1.08
9.	GI Absorption	High	High	High	High
10.	BBB Permeant	No	No	Yes	Yes
11.	Lipinski #violations	0	0	0	0
12.	Veber #Violations	0	0	0	0
13.	Bioavailability score	0.56	0.56	0.55	0.55
14.	Acute toxicity (As per OECD Project)	By i.p. and oral = class 5, by i.v and s.c.= class 4 chemical	By i.p.non toxic, by i.v and oral = class 4, and s.c.= class 5 chemical	By i.p., i.v and oral, s.c. = class 4 chemical	By i.p.- nontoxic in AD, i.v and oral= class 5, s.c.- class 4 chemical

Lipinski rule ad Veber rule are drug likeness rule to determine physicochemical properties of drug. These are set of guidelines used to determine drug like properties of molecule based on its structure. According to Lipinski rule, number of hydrogen bond acceptor should be equal or less than 10, hydrogen bond donor should be equal or less than 5 and molecular weight should be equal or less than 500 dalton. Such molecules are orally active with good solubility having drugability. [7] In our study, we found no violation of Lipinski rule by both test drugs, which highlights drugability of Syringic acid and Sinapic acid. LogP value indicates lipophilicity which is less than 5 indicating goof absorption and permeation of test drugs.[7] Veber rule used to determine bioavailability depending on number of rotatable bonds (less than 10) in the structure and total polar surface area (TPSA less than 140).[8] In our study, we found no violation of Veber rule by both test drugs, which shows good bioavailability of Syringic acid and Sinapic acid. Acute oral toxicity study indicates oral LD50 value more than 5000mg/kg and belongs to class IV and V means test drugs and standard drugs are non toxic and non irritant.

Table 2: Biological and pharmacological activities determined by using Passoline.

Sr. No.	Biological Activity	Neuroprotective Role	Sinapic Acid		Syringic Acid		Gabapentine		Pregabaline	
			Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
1.	Membrane integrity agonist	Useful in traumatic brain injury[9]	0,926	0,837	0,027	0,005	0,663	0,061	0,684	0,058
2.	CYP2J2 substrate	Protective role in PD[10]	0,817	0,696	0,004	0,017	0,894	0,005	0,823	0,016
3.	NADPH peroxidase inhibitor	Reduces microglia-mediated chronic neuroinflammation[11]	0,759	0,781	0,015	0,018	0,799	0,012	0,705	0,026
4.	Phobic disorders treatment	Useful in cognitive behavioural therapy[10]	0,705	0,735	0,060	0,074	0,855	0,015	0,662	0,094
5.	GABA C receptor agonist	Helps to protect the brain in acute stroke[9]	0,611	0,688	0,004	0,005	0,811	0,002	0,696	0,004
6.	Leukotriene-B4 20-monooxygenase inhibitor	Protects against early brain injury[9]	0,580	0,646	0,007	0,014	0,489	0,029	0,530	0,021
7.	Superoxide dismutase inhibitor	Useful in ischemic reperfusion injury, aging and neurodegenerative disease[10]	0,510	0,885	0,004	0,036	0,744	0,010	0,733	0,011
8.	Hydrogen dehydrogenase inhibitor	Useful to treat neurodegenerative diseases[10]	0,509	0,738	0,007	0,039	0,727	0,008	0,715	0,008
9.	G-protein-coupled receptor kinase inhibitor	Useful in PD[10]	0,647	0,704	0,015	0,028	0,714	0,021	0,765	0,016
10.	GABA aminotransferase inhibitor	Useful in neuropsychiatric disorders, epilepsy, addiction[10,11]	0,710	0,586	0,010	0,004	0,575	0,011	0,633	0,007
11.	Neurotransmitter antagonist	Useful in Neurodegenerative diseases[10]	0,503	0,547	0,024	0,039	0,574	0,018	0,505	0,038
12.	Mitochondrial processing peptidase inhibitor	Useful in neurodegenerative Diseases[10]	-	0,736	0,008	-	0,640	0,013	0,729	0,003
13.	Prostaglandin-E2 9-reductase inhibitor	Useful as Neuroprotectant in AD, PD [10]	-	0,704	0,015	-	0,562	0,030	0,703	0,015
14.	Free radical scavenger	Useful as Neuroprotective [11]	0,732	0,619	0,005	0,004	-	-	-	-
15.	TNF expression inhibitor	Useful as Neuroprotective[12,13]	-	0,593	0,014	-	-	-	0,545	0,021
16.	AR expression inhibitor	Useful to treat AD [10]	0,625	0,592	0,014	0,010	-	-	-	-
17.	Glutaminase inhibitor	Useful to treat neuroinflammation[12]	-	0,579	0,004	-	-	-	0,468	0,008
18.	Acetylcholine neuromuscular blocking agent	Useful to treat PD [10]	-	0,566	0,037	-	0,595	0,025	0,583	0,029

Pa indicates probability "to be active", and ***Pi indicates probability "to be inactive"*** [4]. Table No. 2 indicates biological activity of test drugs and standard drugs and these drugs may act as neuroprotective through mentioned biological action. The neuroprotective role of Syringic acid and Sinapic acid and their comparison with gabapentin in peripheral neuropathy is in agreement with our previous published result [13,14,15] . This study highlighted biological activity and target proteins responsible for neuroprotective role of these phenolic acids.

Following possible common target proteins are predicted by using passonline and SwissADME

1. Glycine receptor subunit alpha-1
2. Nuclear receptor subfamily 0 group B member 1
3. Sphingosine 1-phosphate receptor Edg-5
4. Metabotropic glutamate receptor 3

5. Glutamate receptor ionotropic, AMPA 3
6. Carbonic anhydrase III
7. Eukaryotic translation initiation factor 4H
8. Tyrosyl-DNA phosphodiesterase 1
9. Serine/threonine-protein kinase Sgk2
10. Endothelin receptor ET-A
11. Casein kinase I gamma 2
12. Plectin
13. Carbonic anhydrase IV
14. Cytochrome P450 2C9

Table 3 Toxicity profile calculated by using Passonline and Protox II

Target	Gabapentine		Pregabaline		Sinapic acid		Syringic acid	
	Pred	Prob	Pred	Prob	Pred	Prob	Pred	Prob
Hepatotoxicity	Inactive	0.96	Inactive	0.96	Inactive	0.54	Inactive	0.58
Carcinogenicity	**Active**	0.53	Inactive	0.58	Inactive	0.67	Inactive	0.70
Immunotoxicity	Inactive	0.99	Inactive	0.99	Active	0.89	Inactive	0.97
Mutagenicity	Inactive	0.82	Inactive	0.9	Inactive	0.87	Inactive	0.93
Cytotoxicity	Inactive	0.69	Inactive	0.68	Inactive	0.96	Inactive	0.97

**Pred: Prediction; Prob: Probability*

According to above results (Table No.3) test drugs and standard drugs are free of organ toxicity. Gabapentine is seen to be active for carcinogenicity but with less probability.

Figure 1 indicates radar chart of toxicities indicating all these compounds are nonotoxic.

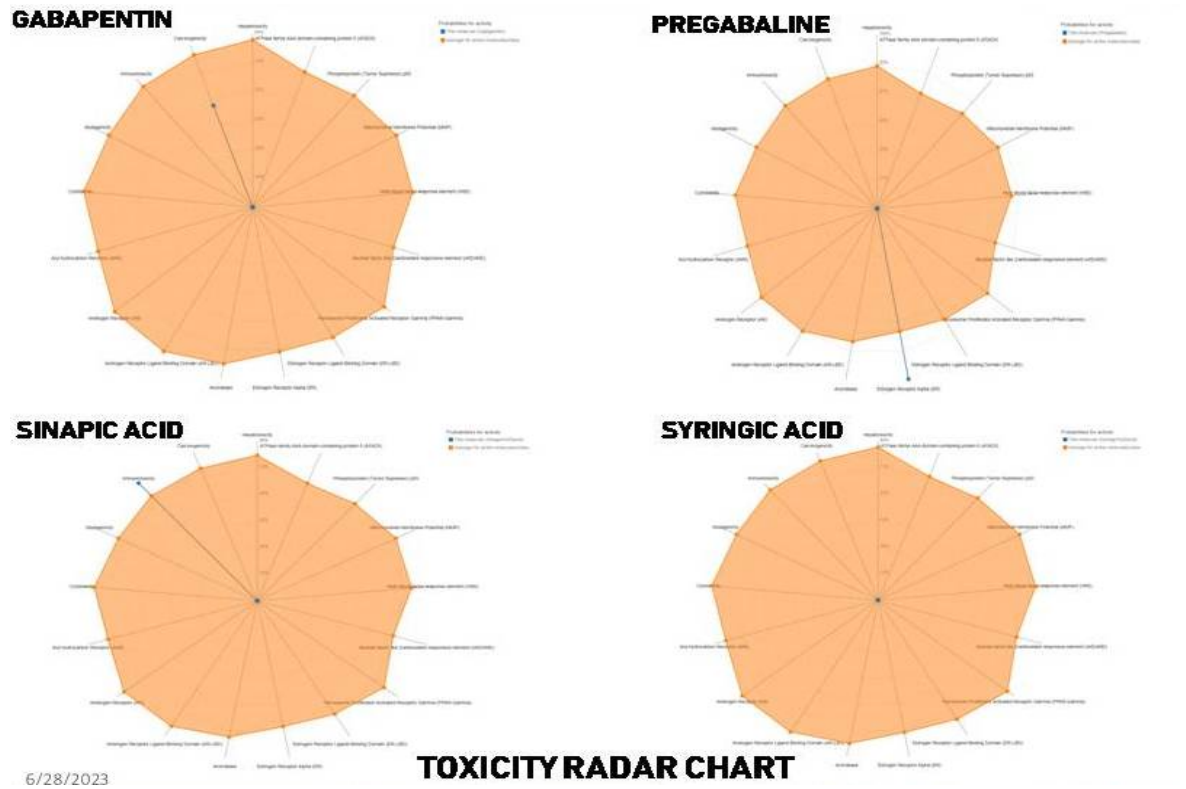

Figure 1: Toxicity radar chart of phenolic acids and standard neuroprotective drugs

CONCLUSION

We have used different softwares i.e. Passonline, SwissADME and Protox II to predict biological activity, pharmacological effects, mechanism of action and toxicity of syringic acid and sinapic acid. This data is compared with standard neuroprotective drugs gabapentin and pregabalin. We found these phenolic acids could be neuroprotective as efficacious as used standard drugs. Syringic acid and Sinapic acid can used clinically for various neuroprotective actions after passing through drug development process.

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CONFLICT OF INTEREST
Authors have no any conflict of interest .

AUTHOR'S CONTRIBUTION
Study conception and design: Shubhangi Pawar and Suvarna Katti; **Data collection**: Shubhangi Pawar and Rupali Patil; **Analysis and interpretation of results:** Suvarna Katti and Manisha Tayde.; **Draft manuscript preparation**: Shubhangi Pawar and Rupali Patil Author. All authors reviewed the results and approved the final version of the manuscript.

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