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EC PHARMACOLOGY AND TOXICOLOGY
Research Article

An *In-silico* Exploration of Possible Nutraceutical Properties of Rice against Multidirectional Attack of Cerebral Ischemia: A Molecular Docking Study of MMP9 and MMP2 Inhibition

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Received: May 01, 2019; **Published:** May 31, 2019

Abstract

Disruption or occlusion in blood supply to brain leads the devastating condition of cerebral ischemia. This reduces oxygen and glucose levels in brain resulting in oxidative stress, inflammation and hence neuronal insult. Matrix metalloproteinases (MMP2 and MMP9), the zinc-dependent endopeptidases, are found to have significantly increased levels in diseased state resulting in excessive breakdown of ECM proteins thus hampering the integrity of blood brain barrier (BBB) and leads to inflammation, infiltration of leukocytes, haemorrhagic transformation and neuronal loss. Rice, a staple crop, has treasure of antioxidant and anti-inflammatory compounds which can combat oxidative stress and inflammation. So, analysis of rice composition on the basis of ADMET properties was done and resulted in 17 capable drug-like compounds then molecular docking was performed between these compounds and potent MMP targets (MMP9 and MMP2) to evaluate the structural inhibition of targets. The docking complexes formed provided high negative binding energies, of -4.4, -5.44, -4.07, -3.96, -4.00, -4.16, -3.63, -4.51, -5.04, -6.08, -7.98, -9.11, -8.10, -6.33, -8.05, -6.96, and 7.72kcal/mol for Ferulic acid, p-Coumaric acid, Sinapic acid, Protocatechuic acid, p-hydroxy benzoic acid, Vanillic acid, Syringic acid, Caffeic acid, Cinnamic acid, Tricin, Luteolin, Apigenin, Quercetin, Isorhamnetin, Kaempferol, Catechin and Epicatechin respectively with MMP9 and -5.06, -5.16, -5.22, -6.25, -6.20, -6.21, -6.17, -4.88, -4.78, -8.96, -8.79, -9.15, -8.07, -8.57, -8.84, -9.08, and -9.17 kcal/mol respectively with MMP2, confirming significant inhibition and hence proving rice a proficient source of treatment for cerebral ischemia.

Keywords: *Cerebral Ischemia; Matrix Metalloproteinase; Rice; Molecular Docking*

Abbreviations

ADMET: Absorption, Distribution, Metabolism, Excretion, Toxicity; BBB: Blood Brain Barrier; ECM: Extracellular Matrix; MMP: Matrix Metalloproteinase; NOS: Nitric Oxide Synthases

Introduction

Cerebral ischemia or ischemic brain injury, the third most pervasive death cause in the world is engulfing millions of lives every year. The complex pathophysiology and high mortality rate of cerebral ischemia grades it under disastrous diseases in USA [1]. It is a condition which arises from interrupted blood supply to brain due to occlusion in arterial blood vessels by thrombus/embolus leading to

reduced oxygen and glucose supply [2,3]. The pathology of cerebral ischemia is highly complex, including excitotoxicity, oxidative stress, blood brain barrier (BBB) dysfunction, inflammation, haemorrhagic transformation and hence excessive neuronal insult [4]. Among its pathophysiological features oxidative stress, BBB dysfunction and inflammation contributes most in the progression of disease hence enhancing the ischemic conditions [3,4].

Oxidative stress is common to all neurodegenerative diseases and is caused due to imbalance between the oxidant free radical species and the antioxidants levels. These free radicals are generally produced in our body but in absence or insufficient amount of antioxidants these free radicals react with the cells or tissues posing great damage to them [4,5]. In cerebral ischemia, excessive production of reactive oxygen species and reactive nitrogen species due to calcium ions overload, inflammation, mitochondrial inhibition and reperfusion injury causes extensive cell death [6]. Superoxide (O_2^-) formed in ischemic condition leads to formation of hydrogen peroxide which is a source of hydroxyl radical [6,7]. Free radicals of nitric oxide are produced from L-arginine by NOS (nitric oxide synthases) activation. Condition of ischemia causes enhancement in activity of NOS (nitric oxide synthases) of type I and type III in neuronal cells and endothelium cells of vasculature. In later stages, NOS II type activity is initiated in glia and neutrophils infiltrated [5,8]. Also such high concentration is capable to overcome the effective detoxifying and scavenging activity of antioxidants present in body like glutathione peroxidase, superoxide dismutase, catalase, vitamin C and glutathione thus enhancing damaging effect on proteins, lipids and DNA content of cells [6,9]. This high free radical concentration in brain along with membrane lipid peroxidation also initiates apoptosis initiating signalling pathways thus causing excessive neuronal insult [8,9]. Many studies have reported use of antioxidants to combat oxidative stress in cerebral ischemia, but profound effects are still left to be attained [9].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases which are activated by cytokines [10,11]. They are involved in remodelling of ECM (extracellular matrix) during normal development and in conditions of inflammation and tissue injury [11,12]. The basement membrane of ECM is made up of proteoglycans and proteins majorly laminin, fibronectin and collagen IV and surrounds the blood vessels as basal lamina in brain [12]. According to researchers, members of MMP family called gelatinase A (MMP2) and gelatinase B (MMP9) have been found to have elevated levels and are responsible for the degradation of collagen IV and fibronectin of the basement membrane thereby leading to BBB disintegration and contribute to ischemic pathology [10-15]. Many researches have experimentally shown the increment in MMP2 and MMP9 levels in animal models and have proved their role in BBB disruption [12-14,16]. Even high levels of MMP9 along with MMP2 were reported in human brain in post-mortem after 2 hrs to many years after experiencing stroke [11]. Rosenberg., *et al*. administered MMP2 in brain and perceived BBB breakage; also, they found a correlation between MMP2 levels and transition of ischemic condition and also in the specificity in BBB opening. They also experimentally prevented BBB proteolysis by administrating MMP inhibitor and reduced haemorrhagic conditions after stroke [16]. Asahi., *et al.* reported reduction in infract volume on administration of MMP inhibitors making their role evident in the diseased state [17]. To contribute to ischemic conditions, the disintegration of BBB via break down of basal lamina by MMPs causes cellular extravasation and loss of integrity of microvasculature resulting into edema, inflammatory cells infiltration, microglial cell activation, hemorrhagic transformation and death of neurona [14-17]. Therefore, on the basis of above facts we can conclude that MMP9 and MMP2 can be considered as potential targets to combat the deleterious disease pathology of cerebral ischemia.

Rice is a staple crop in Asia, and it accounts for 90% of world's rice consumption. Globally, it provides 19% of energy required per person and 13% of protein per person according to 2009 statistics [18]. The miraculous nutraceutical composition of rice provides it outstanding antioxidant and anti-inflammatory properties making it capable to treat variety of health problems [19]. The antioxidant rice composition consists of compounds like flavonoids, phenolic acids, tocotrienols, tocopherols, proanthocyanidins, anthocyanins, phytic acid and γ-oryzanol [19,20]. These antioxidants contribute to cure unhealthy cholesterol levels, stress, hypertension, mental depression, bone problems, immune system malfunctioning and also some skin problems. It also possesses efficiency to treat obesity, cancer, insomnia and neurodegenerative disorders [19,21,22]. To get high levels of antioxidant it is advisable to have whole grain or

bran form of rice [23]. The antioxidant property of phenolic acid is conferred by hydroxyl group on the phenolic rings. The long range of phenolic acids in rice contributes to 7.3 - 8.7milligram per 100gm in endosperm, 20.8-78.3milligram per 100gm in whole grain, 177 - 319 milligram per 100gm in bran and 477.6milligram per 100gm in husk approximately. The composition of phenolic acid consists of ferulic acid, p-coumaric acid, sinapic acid, gallic acid, protocatechuic acid, p-hydroxybenzoic acid, syringic acid and vanillic acid comprising 56 to 76, 8 to 24, 2 to 12, 1 to 4, 1 to 2, 1 and 1% of the total phenolic acid content respectively [19,23,24]. There are many others present in trace amounts as ellagic acid, caffeic acid, chlorogenic acid and cinnamic acid [24]. The flavonoid composition of rice act as antioxidants due to the hydroxyl groups present in phenolic rings especially the 4'OH or the 3'OH. The major flavonoid composition of rice consists of tricin (131.5milligram per 100 gm of flavonoids), luteolin, apigenin, quercetin, isohamnetin, kaempferol and myricetin accounting for 77, 14, 6, 3, 1, less than 1 and less than 1% of the total flavonoids present respectively. There are many others which are not yet confirmed accurately [25,26]. Anthocyanins are glycosides of polymethoxyl and polyhydroxyl of 2 phenylbenzoflavylium or pyrilium salts. Their quantity in whole grain is 345.8 milligram per 100gm and in bran it is 1252 milligram per100gm. In anthocyanins, peonidin-3-glucoside, cyanidin-3-glucoside, cyanidin-3-galactoside and cyanidin-3-rutinoside comprise 6 to 16%, 51 to 81%, 1 to 2% and 3 to 5% of total anthocyanin content respectively. Proanthocyanidins are phenolic polymers having flavonol units. The main proanthocyanidins are catechin and epicatechin and their derivatives having compositional quantity of 20.90milligm and 46.53milligm per 100gm of bran respectively [27,28]. Tocopherol and tocotrienols together known as tocols have basic structure of amphiphilic 6 chromanol ring, which contributes to its antioxidant property, and a sidechain of terpenoid at 2' position of ring. The most abundant of all tocols is γ tocotrienol having 27 to 63% composition then α tocopherol with 10 to 30%, then α tocotrienols 9 to 14% of tocols, δ tocotrienols present in quantity of 2 to 6% of tocols, β tocotrienol 1 to 4%, β tocopherol 1 to 2% and lastly δ tocopherol 1 to 2% approximately [28-30]. An exclusive component of rice is γ oryzanol a blend of steryl ferulates (esters of sterols or alcohols of triterpene with ferulic acid's carboxylic group) contributes a mean composition of 3067milligm per Kg of bran, 288.6 milligm per Kg of whole grain and 58.9milligm per Kg of endosperm [30-32]. The last known component which is active in overcoming oxidative reactions, catalysed by iron, is phytic acid, it contributes to the majority of phosphorus content providing 63% to 73% of total phosphorous. This is the highest contributor of phosphorous in bran which account for about 21.56 milligm per gram [33].

The anti-inflammatory property of rice is also well established a group of researchers have evaluated different variety of rice extract for its anti-inflammatory effect in LPS induced HL60 cells and found effective reduction of pro-inflammatory cytokines like Interlukin-6, TNFα and NFκB [34]. Shalini., *et al.* and Jung., *et al*. independently reported that tricin a major flavonoid in Njavara rice also has anti-inflammatory property [35,36]. Along with antioxidant and anti-inflammatory property, MMP inhibition by rice extracts was also studied on LPS-induced HL60 cells by gelatinase zymography and ELISA assay and this inhibition of MMPs by extract of rice was found to be effective [37,38].

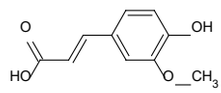
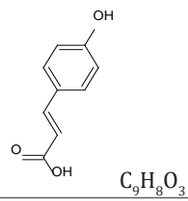
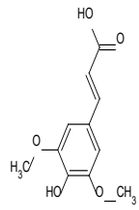
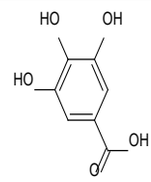
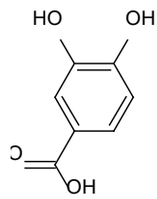
ADMET properties are those which affect the adsorption, distribution, metabolism, excretion and toxicity of drugs *in vivo* [39]. They give idea about the bioavailability and target specificity of a drug. A standard rule of 5 also called Lipinski's rule is a set standard for orally bioavailable drugs which considers molecular weight should be less than 500 Dalton, lipophilicity or Log P should be less than 5, number of hydrogen bond donors should be less than 5 and number of hydrogen bond acceptors should be less than 10 [40]. But for drug targeted to brain the major challenge is to cross the blood brain barrier so some researchers have given more specific standard parameters. The approximate ranges of parameters defined experimentally, which increases chances of a drug to be a potent central nervous system drug are: their Log P value which should be in the range of 1.5 to 2.7, very low or negative lipophilicity will make the drug inefficient to cross BBB and very highly lipophilic drug will retain it in the lipophilic interior of the membrane; the molecular weight should be 400 Da or lesser than that for orally available drug so that they can easily penetrate cellular membranes and also the BBB; the polar surface area should be less than 90°A, the hydrogen bonding heteroatoms should be around 5 or more [41-43]. With the reference of following ranges of parameters effective brain targeted drugs can be analysed.

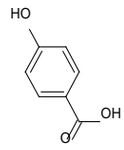
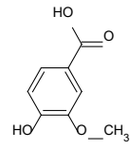
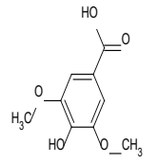
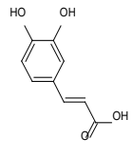
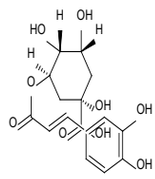
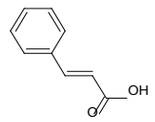
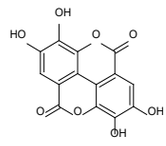
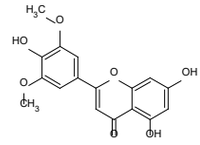
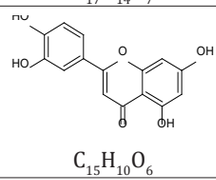
So, one the basis of above facts we hypothesize that rice constituents can act as potent drug to treat cerebral ischemia not only due to their antioxidant and anti-inflammatory properties but also by inhibiting the effective targets like MMP2 and MMP9. To prove our hypothesis, we analysed rice constituents on the basis of their ADMET properties and performed molecular docking between 17 capable constituents of rice and potent cerebral ischemia targets (MMP2 and MMP9) to study structural inhibition of MMPs by rice constituents.

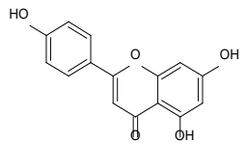
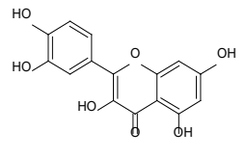
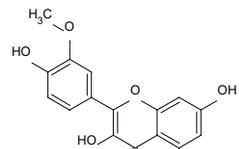
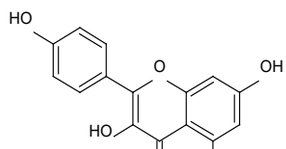
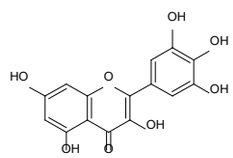
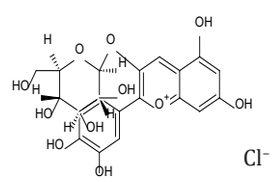
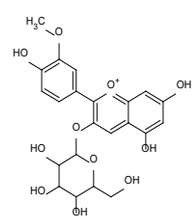
Method

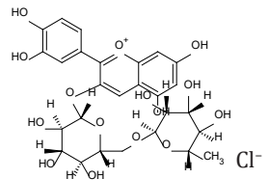
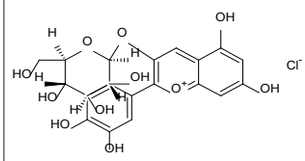
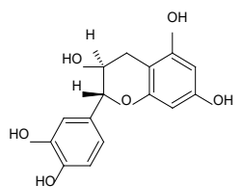
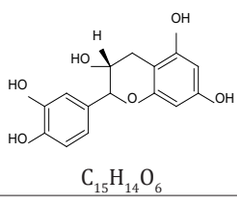
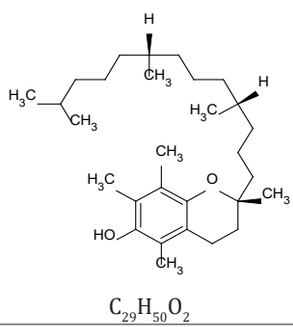
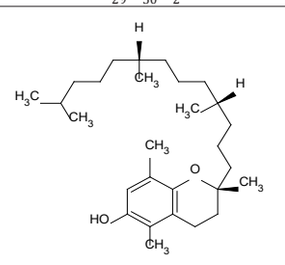
Analysis of rice constituents

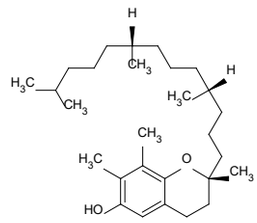
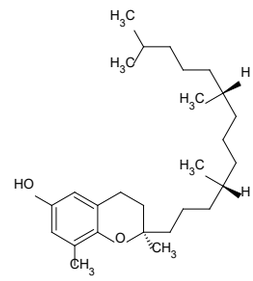
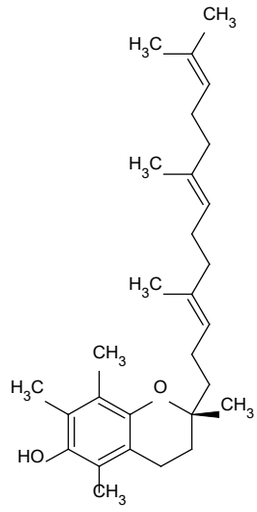
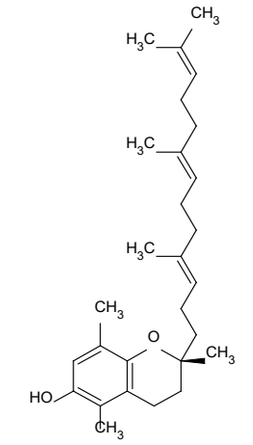
In this study, the smile notations of 35 constituents (Table 1), considered under categories of flavonoids, phenolic acids, tocotrienols, tocopherols, proanthocyanidins, anthocyanins, phytic acid and γ-oryzanol, of rice were gathered from PubChem and their ADMET properties, physiochemical properties and bioactivity scores were calculated by using web based SWISS ADME tool, PROTOX tool and Molinspiration tool [44-46]. Out of the 35 constituents considered, 17 were found to be significant for the purpose of brain targeted drugs by considering Lipinski's rule of 5 as main criteria but molecular weight was considered effective in the range less than 400 Da [40]. In addition the constituents having negative Log P values were considered insignificant as they will be highly hydrophilic and will not be able to cross lipid membranes in their path to targets but neutral or mild hydrophilic compound with very small negative Log P can be considered as in case of cerebral ischemia BBB is disrupted and lipophilicity barrier is less prominent [16,41].

S. No.	Name	Chemical Structure	Molecular wt.	IUPAC	Smile notation
	Phenolic Acid				
1	Ferulic acid	 $C_{10}H_{10}O_4$	194.18 g/mol	(E)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid	COc1cc(ccc1O)/C=C/C(=O)O
2	p-Coumaric acid	 $C_9H_8O_3$	164.16 g/mol	(E)-3-(4-hydroxyphenyl)-2-propenoic acid	C1=CC(=CC=C1\C=C\C(=O)O)O
3	Sinapic acid	 $C_{11}H_{12}O_5$	224.21 g/mol	3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid	COc1cc(cc(c1O)OC)/C=C/C(=O)O
4	Gallic acid	 $C_7H_6O_5$	170.12 g/mol	3,4,5-Trihydroxybenzoic acid	O=C(O)c1cc(O)c(O)c(O)c1
5	Protocatechuic acid	 $C_7H_6O_4$	154.12 g/mol	3,4-Dihydroxybenzoic acid	C1=CC(=C(C=C1C(=O)O)O)O

6	p-hydroxy benzoic acid	 $C_7H_6O_3$	138.12 g/mol	4-Hydroxybenzoic acid	O=C(O)c1ccc(O)cc1
7	Vanillic acid	 $C_8H_8O_4$	168.14 g/mol	4-Hydroxy-3-methoxybenzoic acid	COc1cc(ccc1O)C(=O)O
8	Syringic acid	 $C_9H_{10}O_5$	198.17 g·mol^{-1}	4-Hydroxy-3,5-dimethoxybenzoic acid	COC1=CC(=CC(=C1O)OC)C(=O)O
9	Caffeic acid	 $C_9H_8O_4$	180.16 g/mo	3-(3,4-Dihydroxyphenyl)-2-propenoic acid	O=C(O)\C=C\c1cc(O)c(O)cc1
10	Chlorogenic acid	 $C_{16}H_{18}O_9$	354.31 g/mol	(1*S*,3*R*,4*R*,5*R*)-3-{[(2*E*)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]oxy}-1,4,5-trihydroxycyclohexanecarboxylic acid	O=C(O)[C@]2(O)C[C@@H](O)[C@@H](O)[C@H](OC(=O)\C=C\c1ccc(O)c(O)c1)C2
11	Cinnamic acid	 $C_9H_8O_2$	148.16 g·mol^{-1}	(*E*)-3-phenylprop-2-enoic acid	O=C(O)\C=C\c1ccccc1
12	Ellagic acid	 $C_{14}H_6O_8$	302.197 g/mol	2,3,7,8-Tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10-dione	O=C1Oc3c2c4c1cc(O)c(O)c4OC(=O)c2cc(O)c3O
	Flavanoids				
13	Tricin	 $C_{17}H_{14}O_7$	330.29 g/mol	5,7-dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-4H-chromen-4-one	COC1=CC(=CC(=C1O)OC)C2=CC(=O)C3=C(C=C(C=C3O2)O)O
14	Luteolin	 $C_{15}H_{10}O_6$	286.24 g·mol^{-1}	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O

15	Apigenin	 $C_{15}H_{10}O_5$	270.24 g·mol^{-1}	5,7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one	O=C\1c3c(O/C(=C/1)c2ccc(O)cc2)cc(O)cc3O
16	Quercetin	 $C_{15}H_{10}O_7$	302.236 g/mol	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one	O=C1c3c(O/C(=C1/O)c2ccc(O)c(O)c2)cc(O)cc3O
17	Isorhamnetin	 $C_{16}H_{12}O_7$	316.26 g/mol	3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromen-4-one	COC1=C(C=CC(=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
18	Kaempferol	 $C_{15}H_{10}O_6$	286.23 g/mol	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
19	Myricetin	 $C_{15}H_{10}O_8$	318.24 g·mol^{-1}	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone	Oc1cc(O)c2c(=O)c(O)c(oc2c1)c3cc(O)c(O)c(O)c3
	Anthocyanidins				
20	Cyanidin-3-O-glucoside	 $C_{21}H_{21}O_{11}^{+}$, Cl^{-} $C_{21}H_{21}ClO_{11}$	484.83 g/mol (chloride) 449.38 g/mol	(2S,3R,4S,5S,6R)-2-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-chromenylium-3-yl] oxy-6-(hydroxymethyl) oxane-3,4,5-triol chloride	[Cl-].O(c1c([o+]c2c(c1)c(O)cc(O)c2)c3ccc(O)c(O)c3)[C@@H]4O[C@@H]([C@@H](O)[C@H](O)[C@H]4O)CO
21	Peonidin-3-O-glucoside	 $C_{22}H_{23}O_{11}^{+}$ $C_{22}H_{23}O_{11}Cl$ (chloride)	463.41 g/mol 498.9 g/mol (chloride)	(2S,3R,4S,5S,6R)-2-[5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromenylium-3-yl] oxy-6-(hydroxymethyl) oxane-3,4,5-triol	COC1=C(C=CC(=C1)C2=C(C=C3C(=CC(=CC3=[O+]2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O

22	Cyanidin-3-O-rutinoside	 $C_{27}H_{31}O_{15}$+·Cl-	630.97 g/mol	(2S,3R,4S,5S,6R)-2-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-chromenylium-3-yl] oxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl] oxane-3,4,5-triol chloride	[Cl-].O(C[C@H]4O[C@@H](Oc2cc3c(O)cc(O)cc3[o+]c2c1ccc(O)c(O)c1)[C@H](O)[C@@H](O)[C@@H]4O)[C@@H]5O[C@H]([C@H](O)[C@@H](O)[C@H]5O)C
23	Cyanidin-3-O-galactoside	 $C_{21}H_{21}O_{11}^{+}$, Cl^{-} $C_{21}H_{21}ClO_{11}$	484.83 g/mol (chloride) 449.38 g/mol	(2S,3R,4S,5S,6R)-2-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-chromenylium-3-yl] oxy-6-(hydroxymethyl) oxane-3,4,5-triol chloride	[Cl-].O(c1c([o+]c2c(c1)c(O)cc(O)c2)c3ccc(O)c(O)c3)[C@@H]4O[C@@H]([C@@H](O)[C@H](O)[C@H]4O)CO
	Pro Anthocyanidins				
24	Catechin	 $C_{15}H_{14}O_6$	290.26 g/mol	(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	Oc1ccc(cc1O)[C@H]3Oc2cc(O)cc(O)c2C[C@@H]3O
25	Epicatechin	 $C_{15}H_{14}O_6$	290.26806 g/mol	(3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	C1[C@H](C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
	Tocopherol				
26	α-tocopherol	 $C_{29}H_{50}O_2$	430.7061 g/mol	(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	CC1=C(C(=C2CC[C@@](OC2=C1C)C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C)C)O
27	β-tocopherol	 $C_{28}H_{48}O_2$	416.67952 g/mol	(2R)-2,5,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	CC1=CC(=C(C2=C1O[C@](CC2)(C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C)C)O

28	γ-tocopherol	 $C_{28}H_{48}O_2$	416.67952 g/mol	(2R)-2,7,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	CC1=C(C=C2CC[C@@](OC2=C1C)(C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C)O
29	δ-tocopherol	 $C_{27}H_{46}O_2$	402.65294 g/mol	(2R)-2,8-dimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	CC1=C2C(=CC(=C1)O)CC[C@@](O2)(C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C
	Tocotrienol				
30	α-tocotrienol	 $C_{29}H_{44}O_2$	424.65846 g/mol	(2R)-2,5,7,8-tetramethyl-2-[(3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol	CC1=C(C(=C2CC[C@@](OC2=C1C)(C)CC/C=C(\C)/CC/C=C(\C)/CCC=C(C)C)C)O
31	β-tocotrienol	 $C_{28}H_{42}O_2$	410.63188 g/mol	(2R)-2,5,8-trimethyl-2-[(3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol	CC1=CC(=C(C2=C1O[C@](CC2)(C)CC/C=C(\C)/CC/C=C(\C)/CCC=C(C)C)C)O

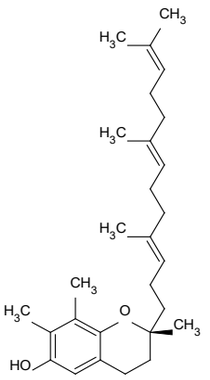
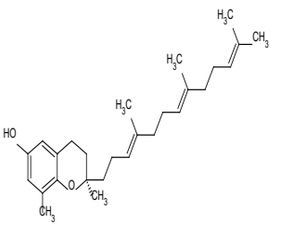
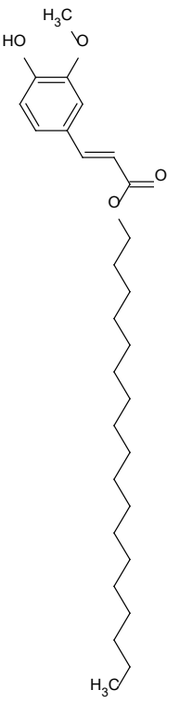
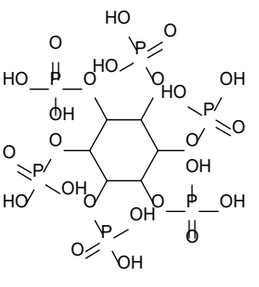
32	γ-tocotrienol	 $C_{28}H_{42}O_2$	410.63188 g/mol	(2R)-2,7,8-trimethyl-2-[(3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol	CC1=C(C=C2CC[C@@](OC2=C1C)(C)CC/C=C(\C)/CC/C=C(\C)/CCC=C(C)C)O
33	δ-tocotrienol	 $C_{27}H_{40}O_2$	396.6053 g/mol	(2R)-2,8-dimethyl-2-[(3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol	CC1=C2C(=CC(=C1)O)CC[C@@](O2)(C)CC/C=C(\C)/CC/C=C(\C)/CCC=C(C)C
34	Steryl ferulate (γ-oryzanol)	 $C_{28}H_{46}O_4$	446.66244 g/mol	octadecyl (E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoate	CCCCCCCCCCCCCCCCCCOC(=O)/C=C/C1=CC(=C(C=C1)O)OC
35	Phytate phosphorus	 $C_6H_{18}O_{24}P_6$	660.035292 g/mol	(2,3,4,5,6-pentaphosphonooxycyclohexyl) dihydrogen phosphate	C1(C(C(C(C(C1OP(=O)(O)O)OP(=O)(O)O)OP(=O)(O)O)OP(=O)(O)O)OP(=O)(O)O

Table 1: *General properties of rice constituents.*

Molecular docking

For molecular docking analysis, the PDB file of all 17 rice constituents (Ferulic acid, p-Coumaric acid, Sinapic acid, Protocatechuic acid, p-hydroxy benzoic acid, Vanillic acid, Syringic acid, Caffeic acid, Cinnamic acid, Tricin, Luteolin, Apigenin, Quercetin, Isorhamnetin, Kaempferol, Catechin and Epicatechin) found significant in above analysis were made by using Online SMILES translator (Online SMILES translator and structure file generator). Open Babel GUI 2.3.2 software was used for chemical file format interconversion where required [48]. The PDB files of MMP2 (PDB ID 1QIB) and MMP9 (PDB ID 1L6J) were obtained from Protein Data Bank. Then molecular docking was performed between these constituents of rice and the potent targets of cerebral ischemia (MMP2 and MMP9) using Autodock Vina software of MGL Tools 1.5.6.

Results

The present study provides an understanding about structural inhibition of prospective targets of cerebral ischemia by rice constituents. To deal with this prospect, a thorough analysis of 35 rice constituents was performed by keeping the physiochemical properties, bioactivity scores and ADMET properties as criteria to investigate their efficiency to act as brain-targeted drug. The detailed outcomes of the following properties for all 35 constituents are provided in Tables 2 to 10. Out of them 17 constituents (Ferulic acid, p-Coumaric acid, Sinapic acid, Protocatechuic acid, p-hydroxy benzoic acid, Vanillic acid, Syringic acid, Caffeic acid, Cinnamic acid, Tricin, Luteolin, Apigenin, Quercetin, Isorhamnetin, Kaempferol, Catechin and Epicatechin) were found to be significant to act as drug. As MMP2 and MMP9 are the most potent targets of cerebral ischemia, structural inhibition analysis of these targets by the above selected constituents was done by molecular docking. The results showed high negative binding energies of the complexes formed in docking, thus demonstrating highly significant inhibition of targets by rice constituents (Table 11). The docking conformations and the hydrogen bonding of rice constituents with MMP9 and MMP2 are provided in figure 1-3.

S. No.	Name	mi LogP	TPSA	n atom	MW	nON	nOHNH	n violation	N rotb	Volume
	Phenolic Acid									
1	Ferulic acid	1.25	66.76	14	194.19	4	2	0	3	172.03
2	p-Coumaric acid	1.43	57.53	12	164.16	3	2	0	2	146.48
3	Sinapic acid	1.26	76	16	224.21	5	2	0	4	197.57
4	Gallic acid	0.59	97.98	12	170.12	5	4	0	1	135.10
5	Protocatechuic acid	0.88	77.75	11	154.12	4	3	0	1	127.08
6	p-hydroxy benzoic acid	1.37	57.53	10	138.12	3	2	0	1	119.06
7	Vanillic acid	1.19	66.76	12	168.15	4	2	0	2	144.61
8	Syringic acid	1.20	76	14	198.17	5	2	0	3	170.15
9	Caffeic acid	0.94	77.75	13	180.16	4	3	0	2	154.50
10	Chlorogenic acid	-0.45	164.74	25	354.31	9	6	1	5	296.27
11	Cinnamic acid	1.91	37.30	11	148.16	2	1	0	2	138.46
12	Ellagic acid	0.94	141.33	22	302.19	8	4	0	0	221.78
	Flavanoids									
13	Tricin	2.30	109.36	24	330.29	7	3	0	3	275.14
14	Luteolin	1.97	111.12	21	286.24	6	4	0	1	232.07
15	Apigenin	2.46	90.89	20	270.24	5	3	0	1	224.05
16	Quercetin	1.68	131.35	22	302.24	7	5	0	1	240.08
17	Isorhamnetin	1.99	120.36	23	316.26	7	4	0	2	257.61
18	Kaempferol	2.17	111.12	21	286.24	6	4	0	1	232.07
19	Myricetin	1.39	151.58	23	318.24	8	6	1	1	248.10
	Anthocyanidins									
20	Cyanidin-3-O-glucoside	-2.79	191.46	32	449.39	11	8	2	4	366.93
21	Peonidin-3-O-glucoside	-2.49	180.47	33	463.42	11	7	2	5	384.46

22	Cyanidin-3-O-rutinoside	-3.49	250.39	42	595.53	15	10	3	6	490.79
23	Cyanidin-3-O-galactoside	-2.79	191.46	32	449.39	11	8	2	4	366.93
	Pro anthocyanidins									
24	Catechin	1.37	110.37	21	290.27	6	5	0	1	244.14
25	Epicatechin	1.37	110.37	21	290.27	6	5	0	1	244.14
	Tocopherol									
26	α-tocopherol	9.04	29.46	31	430.72	2	1	1	12	474.50
27	β-tocopherol	8.98	29.46	30	416.69	2	1	1	12	457.94
28	γ-tocopherol	8.98	29.46	30	416.69	2	1	1	12	457.94
29	δ-tocopherol	8.60	29.46	29	402.66	2	1	1	12	441.38
	Tocotrienol									
30	α-tocotrienol	9.09	29.46	31	424.67	2	1	1	9	455.86
31	β-tocotrienol	9.03	29.46	30	410.64	2	1	1	9	439.30
32	γ-tocotrienol	9.03	29.46	30	410.64	2	1	1	9	439.30
33	δ-tocotrienol	8.67	29.46	29	396.62	2	1	1	9	422.74
34	Steryl ferulate (γoryzanol)	9.22	55.77	32	446.67	4	1	1	21	475.81
35	Phytate phosphorus	-5.55	400.57	36	660.03	24	12	3	12	422.96

Table 2: *Molinspiration physiochemical properties for rice constituents.*

S. No.	Name	Formula	M.W. (g/mol)	No. heavy atoms	No. arom. heavy atoms	Fraction Csp3	No. rotat. bonds	No. H bond acceptors	Num. H-bond donors	Molar Refractivity	TPSA (Å^2)
	Phenolic Acid										
1	Ferulic acid	$C_{10}H_{10}O_4$	194.18	14	6	0.1	3	4	2	51.63	66.76
2	p-Coumaric acid	$C_9H_8O_3$	164.16	12	6	0	2	3	2	45.13	57.53
3	Sinapic acid	$C_{11}H_{12}O_5$	224.21	16	6	0.18	4	5	2	58.12	75.99
4	Gallic acid	$C_7H_6O_5$	170.12	12	6	0	1	5	4	39.47	97.99
5	Protocatechuic acid	$C_7H_6O_4$	154.12	11	6	0	1	4	3	37.45	77.76
6	p-hydroxy benzoic acid	$C_7H_6O_3$	138.12	10	6	0	1	3	2	35.42	57.53
7	Vanillic acid	$C_8H_8O_4$	168.15	12	6	0.12	2	4	2	41.92	66.76
8	Syringic acid	$C_9H_10O_5$	198.17	14	6	0.22	3	5	2	48.41	75.99
9	Caffeic acid	$C_9H_8O_4$	180.16	13	6	0	2	4	3	47.16	77.76
10	Chlorogenic acid	$C_{16}H_{18}O_9$	354.31	25	6	0.38	5	9	6	83.5	164.75
11	Cinnamic acid	$C_9H_8O_2$	148.16	11	6	0	2	2	1	43.11	37.30
12	Ellagic acid	$C_{14}H_6O_8$	302.19	22	16	0	0	8	4	75.31	141.34

	FLAVANOIDS										
13	Tricin	$C_{17}H_{14}O_7$	330.29	24	16	0.12	3	7	3	86.97	109.36
14	Luteolin	$C_{15}H_{10}O_6$	286.24	21	16	0	1	6	4	76.01	111.13
15	Apigenin	$C_{15}H_{10}O_5$	270.24	20	16	0.00	1	5	3	73.99	90.90
16	Quercetin	$C_{15}H_{10}O_7$	302.24	22	16	0	1	7	5	78.03	131.36
17	Isorhamnetin	$C_{16}H_{12}O_7$	316.26	23	16	0.06	2	7	4	82.5	120.36
18	Kaempferol	$C_{15}H_{10}O_6$	286.24	21	16	0	1	6	4	76.01	111.13
19	Myricetin	$C_{15}H_{10}O_8$	318.24	23	16	0	1	8	6	80.06	151.59
	Anthocyanidins										
20	Cyanidin-3-O-glucoside	$C_{21}H_{21}O_{11}$	449.38	32	16	0.29	4	11	8	108.29	193.44
21	Peonidin-3-O-glucoside	$C_{22}H_{23}O_{11}$	463.41	33	16	0.32	5	11	7	112.76	182.44
22	Cyanidin-3-O-rutinoside	$C_{27}H_{31}O_{15}$	595.53	42	16	0.44	6	15	10	139.52	252.36
23	Cyanidin-3-O-galactoside	$C_{21}H_{21}O_{11}$	449.38	32	16	0.29	4	11	8	108.29	193.44
	Pro Anthocy-anidins										
24	Catechin	$C_{15}H_{14}O_6$	290.27	21	12	0.2	1	6	5	74.33	110.38
25	Epicatechin	$C_{15}H_{14}O_6$	290.27	21	12	0.2	1	6	5	74.33	110.38
	Tocopherol										
26	α-tocopherol	$C_{29}H_{50}O_2$	430.71 g/mol	31	6	0.79	12	2	1	139.27	29.46
27	β-tocopherol	$C_{28}H_{48}O_2$	416.68	30	6	0.79	12	2	1	134.31	29.46
28	γ-tocopherol	$C_{28}H_{48}O_2$	416.68	30	6	0.79	12	2	1	134.31	29.46
29	δ-tocopherol	$C_{27}H_{46}O_2$	402.65	29	6	0.78	12	2	1	129.34	29.46
	Tocotrienol										
30	α-tocotrienol	$C_{29}H44O_2$	424.66	31	6	0.59	9	2	1	137.85	29.46
31	β-tocotrienol	$C_{28}H_{42}O_2$	410.63	30	6	0.57	9	2	1	132.88	29.46
32	γ-tocotrienol	$C_{28}H_{42}O_2$	410.63	30	6	0.57	9	2	1	132.88	29.46
33	δ-tocotrienol	$C_{27}H_40O_2$	396.61	29	6	0.56	9	2	1	127.92	29.46
34	Steryl ferulate (γoryzanol)	$C_{28}H_{46}O_4$	446.66	32	6	0.68	21	4	1	137.67	55.76
35	Phytate phosphorus	$C_6H_{18}O_{24}P_6$	660.04	36	0	1	12	24	12	101.27	459.42

Table 3: *Values of physiochemical properties of rice constituents calculated by SWISS-ADME.*

S. No.	Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
	Phenolic acid						
1	Ferulic acid	-0.47	-0.30	-0.72	-0.14	-0.81	-0.12
2	p-Coumaric acid	-0.56	-0.26	-0.91	-0.12	-0.87	-0.15
3	Sinapic acid	-0.32	-0.20	-0.47	-0.03	-0.56	-0.03
4	Gallic acid	-0.77	-0.26	-0.88	-0.52	-0.94	-0.17
5	Protocatechuic acid	-0.88	-0.35	-1.10	-0.58	-1.09	-0.34
6	p-hydroxy benzoic acid	-0.98	-0.39	-1.21	-0.62	-1.19	-0.41
7	Vanillic acid	-0.85	-0.42	-0.99	-0.62	-1.12	-0.35
8	Syringic acid	-0.65	-0.28	-0.69	-0.44	-0.82	-0.15
9	Caffeic acid	-0.48	-0.23	-0.81	-0.10	-0.79	-0.09
10	Chlorogenic acid	0.29	0.14	-0.00	0.74	0.27	0.62
11	Cinnamic acid	-0.74	-0.40	-1.14	-0.47	-0.99	-0.30
12	Ellagic acid	-0.29	-0.27	-0.01	0.11	-0.18	0.17
	Flavanoids						
13	Tricin	-0.06	-0.14	0.23	0.27	-0.18	0.21
14	Luteolin	-0.02	-0.07	0.26	0.39	-0.22	0.28
15	Apigenin	-0.07	-0.09	0.18	0.34	-0.25	-0.26
16	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
17	Isorhamnetin	-0.10	-0.26	0.25	0.28	-0.30	0.22
18	Kaempferol	-0.10	-0.21	0.21	0.32	-0.27	0.26
19	Myricetin	-0.06	-0.18	0.28	0.32	-0.20	0.30
	Anthocyanidins						
20	Cyanidin-3-O-glucoside	0.04	-0.02	0.02	0.11	-0.05	0.26
21	Peonidin-3-O-glucoside	0.00	-0.06	0.01	0.05	-0.11	0.22
22	Cyanidin-3-O-rutinoside	-0.02	-0.40	-0.15	-0.24	-0.05	0.06
23	Cyanidin-3-O-galactoside	0.04	-0.02	0.02	0.11	-0.05	0.26
	Pro anthocyanidins						
24	Catechin	0.41	0.14	0.09	0.60	0.26	0.47
25	Epicatechin	0.41	0.14	0.09	0.60	0.26	0.47
	TOCOPHEROL						
26	α-tocopherol	0.25	0.14	0.21	0.41	0.28	0.24
27	β-tocopherol	0.21	0.09	-0.22	0.45	0.25	0.20
28	γ-tocopherol	0.17	0.06	-0.17	0.40	0.22	0.17
29	δ-tocopherol	0.20	0.09	-0.11	0.44	0.21	0.16
	Tocotrienol						
30	α-tocotrienol	0.26	0.16	-0.23	0.57	0.17	0.38
31	β-tocotrienol	0.23	0.11	-0.24	0.61	0.13	0.35
32	γ-tocotrienol	0.19	0.08	-0.18	0.56	0.10	0.32
33	δ-tocotrienol	0.21	0.11	-0.13	0.61	0.09	0.32
34	Steryl ferulate (γoryzanol)	-0.02	-0.13	-0.14	0.14	-0.06	0.03
35	Phytate phosphorus	0.38	0.44	0.37	0.24	0.31	0.48

Table 4: *Molinspiration bioactivity properties of rice constituents.*

S. No.	Name	Log Po/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
	Phenolic acid						
1	Ferulic acid	1.62	1.51	1.39	1	1.26	1.36
2	p-Coumaric acid	0.95	1.46	1.38	1.28	1.22	1.26
3	Sinapic acid	1.63	1.46	1.4	0.73	1.33	1.31
4	Gallic acid	0.57	0.7	0.5	-0.16	-0.2	0.28
5	Protocatechuic acid	0.66	1.15	0.8	0.4	0.26	0.65
6	p-hydroxy benzoic acid	0.85	1.58	1.09	0.99	0.74	1.05
7	Vanillic acid	1.4	1.43	1.1	0.74	0.73	1.08
8	Syringic acid	1.54	1.04	1.11	0.49	0.77	0.99
9	Caffeic acid	1.07	1.15	1.09	0.7	0.75	0.95
10	Chlorogenic acid	0.82	-0.42	-0.75	-1.05	-0.61	-0.4
11	Cinnamic acid	1.55	2.13	1.68	1.9	1.7	1.79
12	Ellagic acid	0.79	1.1	1.31	0.14	1.67	1
	Flavanoids						
13	Tricin	2.54	3.07	2.59	-0.07	2.59	2.15
14	Luteolin	1.75	2.53	2.28	-0.03	2.03	1.71
15	Apigenin	1.89	3.02	2.58	0.52	2.52	2.11
16	Quercetin	1.61	1.54	1.99	-0.56	1.54	1.22
17	Isorhamnetin	2.35	1.87	2.29	-0.31	2.06	1.65
18	Kaempferol	1.7	1.9	2.28	-0.03	2.03	1.58
19	Myricetin	1.09	1.18	1.69	-1.08	1.06	0.79
	Anthocyanidins						
20	Cyanidin-3-O-glucoside	-1.31	-1.03	0.38	-1.76	-1.91	-1.13
21	Peonidin-3-O-glucoside	-1.43	-0.71	0.69	-1.54	-1.37	-0.87
22	Cyanidin-3-O-rutinoside	-1.24	-1.51	-0.77	-3.08	-3.43	-2.01
23	Cyanidin-3-O-galactoside	-1.42	-1.03	0.38	-1.76	-1.91	-1.15
	Pro Anthocyanidins						
24	Catechin	1.33	0.36	1.22	0.24	0.98	0.83
25	Epicatechin	1.47	0.36	1.22	0.24	0.98	0.85
	Tocopherol						
26	α-tocopherol	5.92	10.70	8.84	6.14	9.75	8.27
27	β-tocopherol	5.67	10.33	8.53	5.94	9.2	7.93
28	γ-tocopherol	5.24	10.33	8.53	5.94	9.2	7.85
29	δ-tocopherol	5.65	9.97	8.22	5.74	8.65	7.65
	Tocotrienol						
30	α-tocotrienol	5.71	9.31	8.6	5.88	9.27	7.75
31	β-tocotrienol	5.64	8.94	8.29	5.68	8.71	7.45
32	γ-tocotrienol	5.26	8.94	8.29	5.68	8.71	7.38
33	δ-tocotrienol	5.04	8.58	7.98	5.48	8.16	7.05
34	Steryl ferulate (γoryzanol)	6.51	10.67	8.11	5.24	8.83	7.87
35	Phytate phosphorus	-5.21	-10.28	-3.13	-7.36	-8.29	-6.85

Table 5: *Values of lipophilicity parameters of rice constituents calculated by SWISS ADME.*

S. No.	Name	Pains	Brenk	Leadlikeness	Synthetic accessibility
	Phenolic Acid				
1	Ferulic acid	0 alert	1 alert: michael_ acceptor_1	No; 1 violation: MW < 250	1.93
2	p-Coumaric acid	0 alert	1 alert: michael_ acceptor_1	No; 1 violation: MW < 250	1.61
3	Sinapic acid	0 alert	1 alert: michael_ acceptor_1	No; 1 violation: MW < 250	2.17
4	Gallic acid	1 alert: catechol_A	1 alert: catechol	No; 1 violation: MW < 250	1.22
5	Protocatechuic acid	1 alert: catechol_A	1 alert: catechol	No; 1 violation: MW < 250	1.07
6	p-hydroxy benzoic acid	0 alert	0 alert	No; 1 violation: MW < 250	1
7	Vanillic acid	0 alert	0 alert	No; 1 violation: MW < 250	1.42
8	Syringic acid	0 alert	0 alert	No; 1 violation: MW < 250	1.7
9	Caffeic acid	1 alert: catechol_A	2 alerts: catechol, michael_acceptor_1	No; 1 violation: MW < 250	1.81
10	Chlorogenic acid	1 alert: catechol_A	2 alerts: catechol, michael_acceptor_1	No; 1 violation: MW > 350	4.16
11	Cinnamic acid	0 alert	1 alert: michael_acceptor_1	No; 1 violation: MW < 250	1.67
12	Ellagic acid	1 alert: catechol_A	3 alerts: catechol, cumarine, polycyclic_ aromatic_hydrocarbon_3	Yes	3.17
	Flavanoids				
13	Tricin	0 alert	0 alert	Yes	3.21
14	Luteolin	1 alert: catechol_A	1 alert: catechol	Yes	3.02
15	Apigenin	0 alert	0 alert	Yes	2.96
16	Quercetin	1 alert: catechol_A	1 alert: catechol	Yes	3.23
17	Isorhamnetin	0 alert	0 alert	Yes	3.26
18	Kaempferol	0 alert	0 alert	Yes	3.14
19	Myricetin	1 alert: catechol_A	1 alert: catechol	Yes	3.27
	Anthocyanidins				
20	Cyanidin-3-O-glucoside	1 alert: catechol_A	2 alerts: catechol, charged_oxygen_sulfur	No; 1 violation: MW > 350	5.27
21	Peonidin-3-O-glucoside	0 alert	1 alert: charged_ oxygen_sulfur	No; 1 violation: MW > 350	5.38
22	Cyanidin-3-O-rutinoside	1 alert: catechol_A	2 alert: catechol, charged_oxygen _sulfur	No; 1 violation: MW > 350	6.47
23	Cyanidin-3-O-galacto-side	1 alert: catechol_A	2 alerts: catechol, charged_oxygen_sulfur	No; 1 violation: MW > 350	5.27
	Pro anthocyanidins				
24	Catechin	1 alert: catechol_A	1 alert: catechol	Yes	3.5
25	Epicatechin	1 alert: catechol_A	1 alert: catechol	Yes	3.5
	Tocopherol				
26	α-tocopherol	0 alert	0 alert	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	5.17

27	β-tocopherol	0 alert	0 alert	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	5.06
28	γ-tocopherol	0 alert	0 alert	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	5
29	δ-tocopherol	0 alert	0 alert	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.88
	Tocotrienol				
30	α-tocotrienol	0 alert	1 alert: isolated_alkene	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.63
31	β-tocotrienol	0 alert	1 alert: isolated_alkene	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.51
32	γ-tocotrienol	0 alert	1 alert: isolated_alkene	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.47
33	δ-tocotrienol	0 alert	1 alert: isolated_alkene	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.36
34	Steryl ferulate (γoryzanol)	0 alert	1 alert: michael_acceptor_1	No; 3 violations: MW > 350, Rotors > 7, XLOGP3 > 3.5	4.18
35	Phytate phosphorus	0 alert	1 alert: phosphor	No; 2 violations: MW > 350, Rotors > 7	5.86

Table 6: *Values of medical chemistry parameters of rice constituents by SWISS ADME.*

S. No.	Name	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
	Phenolic Acid						
1	Ferulic acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.56
2	p-Coumaric acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.56
3	Sinapic acid	Yes; 0 violation	Yes	Yes	Yes	Yes	0.56
4	Gallic acid	Yes; 0 violation	No; 2 violations: MR<40, #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.56
5	Protocatechuic acid	Yes; 0 violation	No; 3 violations: MW<160, MR<40, #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.56
6	p-hydroxy benzoic acid	Yes; 0 violation	No; 3 violations: MW<160, MR<40, #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.56
7	Vanillic acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.56
8	Syringic acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.56
9	Caffeic acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.56
10	Chlorogenic acid	Yes; 1 violation: H-don>5	No; 1 violation: WLOGP<-0.4	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violations: TPSA>150, H-don>5	0.11
11	Cinnamic acid	Yes; 0 violation	No; 2 violations: MW<160, #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.56

12	Ellagic acid	Yes; 0 violation	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	Yes	0.55
	Flavanoids						
13	Tricin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
14	Luteolin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
15	Apigenin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
16	Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
17	Isorhamnetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
18	Kaempferol	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
19	Myricetin	Yes; 1 violation: H-don>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violations: TPSA>150, H-don>5	0.55
	Anthocyanidins						
20	Cyanidin-3-O-glucoside	No; 2 violations: H-acc>10, H-don>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 3 violations: TPSA>150, H-acc>10, H-don>5	0.17
21	Peonidin-3-O-glucoside	No; 2 violations: H-acc>10, H-don>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA> 131.6	No; 3 violations: TPSA>150, H-acc>10, H-don>5	0.17
22	Cyanidin-3-O-rutinoside	No;3 violations: MW>500, H-acc>10, H-don>5	No; 4 violations: MW>480, WLOGP<-0.4, MR>130,# atoms>70	No; 1 violation: TPSA >140	No; 1 violation: TPSA> 131.6	No; 3 violations: TPSA >150, H-acc>10, H-don>5	0.17
23	Cyanidin-3-O-galactoside	No; 2 violations: H-acc>10, H-don>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 3 violations: TPSA>150, H-acc>10, H-don>5	0.17
	Pro Anthocyanidins						
24	Catechin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
25	Epicatechin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
	Tocopherol						
26	α-tocopherol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
27	β-tocopherol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55

28	γ-tocopherol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
29	δ-tocopherol	Yes; 1 violation: MLOGP>4.15	No; 2 violations: WLOGP>5.6, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
	Tocotrienol						
30	α-tocotrienol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
31	β-tocotrienol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
32	γ-tocotrienol	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
33	δ-tocotrienol	Yes; 1 violation: MLOGP>4.15	No; 1 violation: WLOGP>5.6	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.55
34	Steryl ferulate (γoryzanol)	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 1 violation: Rotors>10	No; 1 violation: WLOGP>5.88	No; 2 violations: XLOGP3>5, Rotors>15	0.55
35	Phytate phosphorus	No; 3 violations: MW>500, H-acc>10, H-don>5	No; 2 violations: MW>480, WLOGP<-0.4	No; 2 violations: Rotors>10, TPSA>140	No; 1 violation: TPSA>131.6	No; 5 violations: MW>600, XLOGP3<-2, TPSA>150, H-acc>10, H-don>5	0.11

Table 7: *Values of drug likeness parameters of rice constituents by SWISS ADME.*

S. No.	Name	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	LogKp (skin permeation cm/s)
	Phenolic Acid									
1	Ferulic acid	High	Yes	No	No	No	No	No	No	-6.41
2	p-Coumaric acid	High	Yes	No	No	No	No	No	No	-6.26
3	Sinapic acid	High	No	No	No	No	No	No	No	-6.63
4	Gallic acid	High	No	No	No	No	No	No	Yes	-6.84
5	Protocatechuic acid	High	No	No	No	No	No	No	Yes	-6.42
6	p-hydroxy benzoic acid	High	Yes	No	No	No	No	No	No	-6.02
7	Vanillic acid	High	No	No	No	No	No	No	No	-6.31
8	Syringic acid	High	No	No	No	No	No	No	No	-6.77
9	Caffeic acid	High	No	No	No	No	No	No	No	-6.58
10	Chlorogenic acid	Low	No	No	No	No	No	No	No	-8.76

11	Cinnamic acid	High	Yes	No	No	No	No	No	No	-5.69
12	Ellagic acid	High	No	No	Yes	No	No	No	No	-7.36
	Flavanoids									
13	Tricin	High	No	No	Yes	No	Yes	Yes	Yes	-6.14
14	Luteolin	High	No	No	Yes	No	No	Yes	Yes	-6.25
15	Apigenin	High	No	No	Yes	No	No	Yes	Yes	-5.80
16	Quercetin	High	No	No	Yes	No	No	Yes	Yes	-7.05
17	Isorhamnetin	High	No	No	Yes	No	No	Yes	Yes	-6.90
18	Kaempferol	High	No	No	Yes	No	No	Yes	Yes	-6.70
19	Myricetin	Low	No	No	Yes	No	No	No	Yes	-7.40
	Anthocyanidins									
20	Cyanidin-3-O-glucoside	Low	No	No	No	No	No	No	No	-9.77
21	Peonidin-3-O-glucoside	Low	No	No	No	No	No	No	No	-9.63
22	Cyanidin-3-O-rutinoside	Low	No	No	No	No	No	No	No	-11.00
23	Cyanidin-3-O-galactoside	Low	No	No	No	No	No	No	No	-9.77
	Pro Anthocyanidins									
24	Catechin	High	No	Yes	No	No	No	No	No	-7.82
25	Epicatechin	High	No	Yes	No	No	No	No	No	-7.82
	Tocopherol									
26	α-tocopherol	Low	No	Yes	No	No	No	No	No	-1.33
	β-tocopherol	Low	No	Yes	No	No	No	No	No	-1.51
28	γ-tocopherol	Low	No	Yes	No	No	No	No	No	-1.51
29	δ-tocopherol	Low	No	Yes	No	No	No	No	No	-1.68
	Tocotrienol									
30	α-tocotrienol	Low	No	Yes	No	No	No	No	No	-2.28
31	β-tocotrienol	Low	No	Yes	No	No	No	No	No	-2.46
32	γ-tocotrienol	Low	No	Yes	No	No	No	No	No	-2.46
33	δ-tocotrienol	Low	No	Yes	No	No	No	No	Yes	-2.63
34	Steryl ferulate (γoryzanol)	Low	No	No	No	Yes	No	No	No	-1.45
35	Phytate phosphorus	Low	No	Yes	No	No	No	No	No	-17.63

Table 8: *Values of pharmacokinetics parameters of rice constituents calculated by SWISS ADME.*

S. No.	Name	Log S (ESOL)	Solubility	Class	Log S (Ali)	Solubility	Class	Log S (SILICOS-IT)	Solubility	Class
	Phenolic Acid									
1	Ferulic acid	-2.11	1.49e+00 mg/ml ; 7.68e-03 mol/l	Soluble	-2.52	5.86e-01 mg/ml ; 3.02e-03 mol/l	Soluble	-1.42	7.43e+00 mg/ml ; 3.83e-02 mol/l	Soluble
2	p-Coumaric acid	-2.02	1.58e+00 mg/ml ; 9.65e-03 mol/l	Soluble	-2.27	8.73e-01 mg/ml ; 5.32e-03 mol/l	Soluble	-1.28	8.67e+00 mg/ml ; 5.28e-02 mol/l	Soluble
3	Sinapic acid	-2.16	1.54e+00 mg/ml ; 6.86e-03 mol/l	Soluble	-2.66	4.88e-01 mg/ml ; 2.18e-03 mol/l	Soluble	-1.55	6.33e+00 mg/ml ; 2.82e-02 mol/l	Soluble
4	Gallic acid	-1.64	3.90e+00 mg/ml ; 2.29e-02 mol/l	Very soluble	-2.34	7.86e-01 mg/ml ; 4.62e-03 mol/l	Soluble	-0.04	1.55e+02 mg/ml ; 9.10e-01 mol/l	Soluble
5	Protocatechuic acid	-1.86	2.14e+00 mg/ml ; 1.39e-02 mol/l	Very soluble	-2.38	6.46e-01 mg/ml ; 4.19e-03 mol/l	Soluble	-0.6	3.83e+01 mg/ml ; 2.48e-01 mol/l	Soluble
6	p-hydroxy benzoic acid	-2.07	1.18e+00 mg/ml ; 8.52e-03 mol/l	Soluble	-2.4	5.51e-01 mg/ml ; 3.99e-03 mol/l	Soluble	-1.17	9.40e+00 mg/ml ; 6.81e-02 mol/l	Soluble
7	Vanillic acid	-2.02	1.60e+00 mg/ml ; 9.52e-03 mol/l	Soluble	-2.44	6.15e-01 mg/ml ; 3.66e-03 mol/l	Soluble	-1.32	8.10e+00 mg/ml ; 4.82e-02 mol/l	Soluble
8	Syringic acid	-1.84	2.84e+00 mg/ml ; 1.44e-02 mol/l	Very soluble	-2.23	1.18e+00 mg/ml ; 5.94e-03 mol/l	Soluble	-1.46	6.93e+00 mg/ml ; 3.50e-02 mol/l	Soluble
9	Caffeic acid	-1.89	2.32e+00 mg/ml ; 1.29e-02 mol/l	Very soluble	-2.38	7.55e-01 mg/ml ; 4.19e-03 mol/l	Soluble	-0.71	3.51e+01 mg/ml ; 1.95e-01 mol/l	Soluble
10	Chlorogenic acid	-1.62	8.50e+00 mg/ml ; 2.40e-02 mol/l	Very soluble	-2.58	9.42e-01 mg/ml ; 2.66e-03 mol/l	Soluble	0.4	8.94e+02 mg/ml ; 2.52e+00 mol/l	Soluble
11	Cinnamic acid	-2.37	6.29e-01 mg/ml ; 4.25e-03 mol/l	Soluble	-2.54	4.23e-01 mg/ml ; 2.85e-03 mol/l	Soluble	-1.84	2.14e+00 mg/ml ; 1.45e-02 mol/l	Soluble
12	Ellagic acid	-2.94	3.43e-01 mg/ml ; 1.14e-03 mol/l	Soluble	-3.66	6.60e-02 mg/ml ; 2.18e-04 mol/l	Soluble	-3.35	1.36e-01 mg/ml ; 4.49e-04 mol/l	Soluble
	Flavanoids									
13	Tricin	-4.12	2.52e-02 mg/ml ; 7.63e-05 mol/l	Mod-erately soluble	-5.03	3.06e-03 mg/ml ; 9.26e-06 mol/l	Mod-erately soluble	-4.63	7.71e-03 mg/ml ; 2.33e-05 mol/l	Mod-erately soluble
14	Luteolin	-3.71	5.63e-02 mg/ml ; 1.97e-04 mol/l	Soluble	-4.51	8.84e-03 mg/ml ; 3.09e-05 mol/l	Mod-erately soluble	-3.82	4.29e-02 mg/ml ; 1.50e-04 mol/l	Soluble
15	Apigenin	-3.94	3.07e-02 mg/ml; 1.14e-04 mol/l	Soluble	-4.59	6.88e-03 mg/ml; 2.55e-05 mol/l	Mod-erately soluble	-4.40	1.07e-02mg/ml; 3.94e-05mol/l	Mod-erately soluble
16	Quercetin	-3.16	2.11e-01 mg/ml ; 6.98e-04 mol/l	Soluble	-3.91	3.74e-02 mg/ml ; 1.24e-04 mol/l	Soluble	-3.24	1.73e-01 mg/ml ; 5.73e-04 mol/l	Soluble
17	Isorhamnetin	-3.36	1.38e-01 mg/ml ; 4.35e-04 mol/l	Soluble	-4.02	3.03e-02 mg/ml ; 9.57e-05 mol/l	Mod-erately soluble	-3.94	3.65e-02 mg/ml ; 1.15e-04 mol/l	Soluble
18	Kaempferol	-3.31	1.40e-01 mg/ml ; 4.90e-04 mol/l	Soluble	-3.86	3.98e-02 mg/ml ; 1.39e-04 mol/l	Soluble	-3.82	4.29e-02 mg/ml ; 1.50e-04 mol/l	Soluble

19	Myricetin	-3.01	3.14e-01 mg/ml ; 9.88e-04 mol/l	Soluble	-3.96	3.50e-02 mg/ml ; 1.10e-04 mol/l	Soluble	-2.66	6.98e-01 mg/ml ; 2.19e-03 mol/l	Soluble
	Anthocyanidins									
20	Cyanidin-3-O-glucoside	-2.08	3.71e+00 mg/ml ; 8.25e-03 mol/l	Soluble	-2.54	1.28e+00 mg/ml ; 2.85e-03 mol/l	Soluble	-0.93	5.23e+01 mg/ml ; 1.16e-01 mol/l	Soluble
21	Peonidin-3-O-glucoside	-2.29	2.35e+00mg/ml; 5.07e-03 mol/l	soluble	-2.65	1.05e+00mg/ml; 2.26e-03 mol/l	soluble	-1.62	1.11e+01 mg/ml; 2.39e-02mol/l	soluble
22	Cyanidin-3-O-rutinoside	-2.47	2.03e+00 mg/ml; 3.41e-03mol/l	soluble	-3.28	3.10e-01 mg/ml; 5.20e-04mol/l	soluble	0.28	1.15e+03 mg/ml; 1.92e+00mol/l	soluble
23	Cyanidin-3-O-galactoside	-2.08	3.71e+00 mg/ml ; 8.25e-03 mol/l	Soluble	-2.54	1.28e+00 mg/ml ; 2.85e-03 mol/l	Soluble	-0.93	5.23e+01 mg/ml ; 1.16e-01 mol/l	Soluble
	Pro Anthocyanidins									
24	Catechin	-2.22	1.74e+00 mg/ml ; 5.98e-03 mol/l	Soluble	-2.24	1.66e+00 mg/ml ; 5.72e-03 mol/l	Soluble	-2.14	2.09e+00 mg/ml ; 7.19e-03 mol/l	Soluble
25	Epicatechin	-2.22	1.74e+00 mg/ml ; 5.98e-03 mol/l	Soluble	-2.24	1.66e+00 mg/ml ; 5.72e-03 mol/l	Soluble	-2.14	2.09e+00 mg/ml ; 7.19e-03 mol/l	Soluble
	Tocopherol									
26	α-tocopherol	-8.60	1.08e-06 mg/ml; 2.50e-09 mol/l	Poorly soluble	-11.27	2.30e-09 mg/ml; 5.33e-12 mol/l	Insoluble	-9.16	2.97e-07 mg/ml ; 6.89e-10 mol/l	Poorly soluble
27	β-tocopherol	-8.29	2.15e-06 mg/ml ; 5.16e-09 mol/l	Poorly soluble	-10.89	5.38e-09 mg/ml ; 1.29e-11 mol/l	Insoluble	-8.79	6.80e-07 mg/ml ; 1.63e-09 mol/l	Poorly soluble
28	γ-tocopherol	-8.29	2.15e-06 mg/ml ; 5.16e-09 mol/l	Poorly soluble	-10.89	5.38e-09 mg/ml ; 1.29e-11 mol/l	Insoluble	-8.79	6.80e-07 mg/ml ; 1.63e-09 mol/l	Poorly soluble
29	δ-tocopherol	-7.98	4.23e-06 mg/ml ; 1.05e-08 mol/l	Poorly soluble	-10.52	1.23e-08 mg/ml ; 3.05e-11 mol/l	Insoluble	-8.41	1.56e-06 mg/ml ; 3.86e-09 mol/l	Poorly soluble
	Tocotrienol									
30	α-tocotrienol	-7.89	5.50e-06 mg/ml ; 1.30e-08 mol/l	Poorly soluble	-9.83	6.27e-08 mg/ml ; 1.48e-10 mol/l	Poorly soluble	-8.08	3.56e-06 mg/ml ; 8.38e-09 mol/l	Poorly soluble
31	β-tocotrienol	-7.57	1.10e-05 mg/ml ; 2.68e-08 mol/l	Poorly soluble	-9.45	1.47e-07 mg/ml ; 3.57e-10 mol/l	Poorly soluble	-7.7	8.14e-06 mg/ml ; 1.98e-08 mol/l	Poorly soluble
32	γ-tocotrienol	-7.57	1.10e-05 mg/ml ; 2.68e-08 mol/l	Poorly soluble	-9.45	1.47e-07 mg/ml ; 3.57e-10 mol/l	Poorly soluble	-7.7	8.14e-06 mg/ml ; 1.98e-08 mol/l	Poorly soluble
33	δ-tocotrienol	-7.26	2.16e-05 mg/ml ; 5.45e-08 mol/l	Poorly soluble	-9.07	3.35e-07 mg/ml ; 8.45e-10 mol/l	Poorly soluble	-7.33	1.86e-05 mg/ml ; 4.70e-08 mol/l	Poorly soluble
34	Steryl ferulate (γoryzanol)	-8.08	3.68e-06 mg/ml ; 8.24e-09 mol/l	Poorly soluble	-11.79	7.17e-10 mg/ml ; 1.61e-12 mol/l	Insoluble	-8.88	5.94e-07 mg/ml ; 1.33e-09 mol/l	Poorly soluble
35	Phytate phosphorus	3.34	1.43e+06 mg/ml ; 2.17e+03 mol/l	Highly soluble	1.47	1.94e+04 mg/ml ; 2.94e+01 mol/l	Highly soluble	8.57	2.45e+11 mg/ml ; 3.71e+08 mol/l	Soluble

Table 9: *Values of water solubility parameters of rice constituents calculated by SWISS ADME.*

S. No.	Name	LD50 mg/Kg	Toxicity Class	Potential toxicity targets
	Phenolic Acid			
1	Ferulic acid	1772	4	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
2	p-Coumaric acid	2850	5	Prostaglandin G/H synthase 1
3	Sinapic acid	1772	4	Amine oxidase A, Prostaglandin G/H synthase 1
4	Gallic acid	2000	4	Androgen receptor
5	Protocatechuic acid	2000	4	Androgen receptor
6	p-hydroxy benzoic acid	2200	5	Androgen receptor, Prostaglandin G/H synthase 1
7	Vanillic acid	2000	4	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
8	Syringic acid	1700	4	Androgen receptor, Prostaglandin G/H synthase 1
9	Caffeic acid	2980	5	Prostaglandin G/H synthase 1
10	Chlorogenic acid	5000	5	Amine oxidase A, Prostaglandin G/H synthase 1
11	Cinnamic acid	2500	5	Prostaglandin G/H synthase 1
12	Ellagic acid	2991	4	Prostaglandin G/H synthase 1
	Flavanoids			
13	Tricin	4000	5	Androgen receptor, Amine oxidase A, Estrogen receptor 2, Prostaglandin G/H synthase 1
14	Luteolin	3919	5	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
15	Apigenin	2500	5	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
16	Quercetin	159	3	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
17	Isorhamnetin	5000	5	Androgen receptor, Amine oxidase A, Estrogen receptor 2, Prostaglandin G/H synthase 1
18	Kaempferol	3919	5	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
19	Myricetin	159	3	Androgen receptor, Amine oxidase A, Prostaglandin G/H synthase 1
	Anthocyanidins			
20	Cyanidin-3-O-glucoside	5000	5	Androgen receptor beta 2, Prostaglandin G/H synthase 1
21	Peonidin-3-O-glucoside	5000	5	Androgen receptor beta 2, Prostaglandin G/H synthase 1
22	Cyanidin-3-O-rutinoside	5000	5	Androgen receptor beta 2, Prostaglandin G/H synthase 1
23	Cyanidin-3-O-galactoside	5000	5	Androgen receptor beta 2, Prostaglandin G/H synthase 1
	Pro anthocyanidins			
24	Catechin	10000	6	Prostaglandin G/H synthase 1
25	Epicatechin	10000	6	Prostaglandin G/H synthase 1
	Tocopherol			
26	α-tocopherol	5000	5	Amine oxidase A, Prostaglandin G/H synthase 1
27	β-tocopherol	5000	5	Amine oxidase A, Prostaglandin G/H synthase 1
28	γ-tocopherol	5000	5	Amine oxidase A, Prostaglandin G/H synthase 1
29	δ-tocopherol	5000	5	Amine oxidase A, Prostaglandin G/H synthase 1
	Tocotrienol			
30	α-tocotrienol	500	4	Amine oxidase A
31	β-tocotrienol	500	4	Amine oxidase A
32	γ-tocotrienol	500	4	Amine oxidase A
33	δ-tocotrienol	500	4	Amine oxidase A
34	Steryl ferulate (γoryzanol)	9600	6	Amine oxidase A, Prostaglandin G/H synthase 1
35	Phytate phosphorus	1500	4	No toxicity target

Table 10: *Values of toxicity parameters of rice constituents calculated by PROTOX.*

S. No.	Component of rice	MMP9 (1L6J) ΔG (kcal/mol)	MMP2 (1QIB) ΔG (kcal/mol)
1	Ferulic acid	-4.4	-5.06
2	p-Coumaric acid	-5.44	-5.16
3	Sinapic acid	-4.07	-5.22
4	Protocatechuic acid	-3.96	-6.25
5	p-hydroxy benzoic acid	-4.00	-6.20
6	Vanillic acid	-4.16	-6.21
7	Syringic acid	-3.63	-6.17
8	Caffeic acid	-4.51	-4.88
9	Cinnamic acid	-5.04	-4.78
10	Tricin	-6.08	-8.96
11	Luteolin	-7.98	-8.79
12	Apigenin	-9.11	-9.15
13	Quercetin	-8.1	-8.07
14	Isorhamnetin	-6.33	-8.57
15	Kaempferol	-8.05	-8.84
16	Catechin	-6.96	-9.08
17	Epicatechin	-7.72	-9.17

Table 11: *Binding energy results of molecular docking complexes of rice constituents with MMP9 and MMP2.*

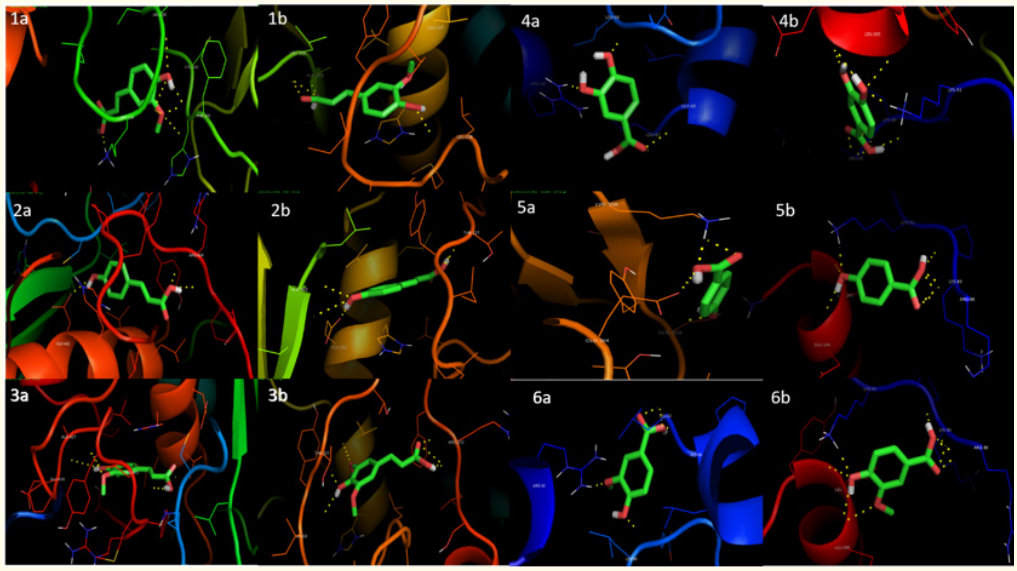


Figure 1: *Docking conformations of a) MMP9 b) MMP2 with 1. Ferulic acid 2. p-Coumaric acid 3. Sinapic acid 4. Protocatechuic acid 5. p-hydroxy benzoic acid 6. Vanillic acid.*

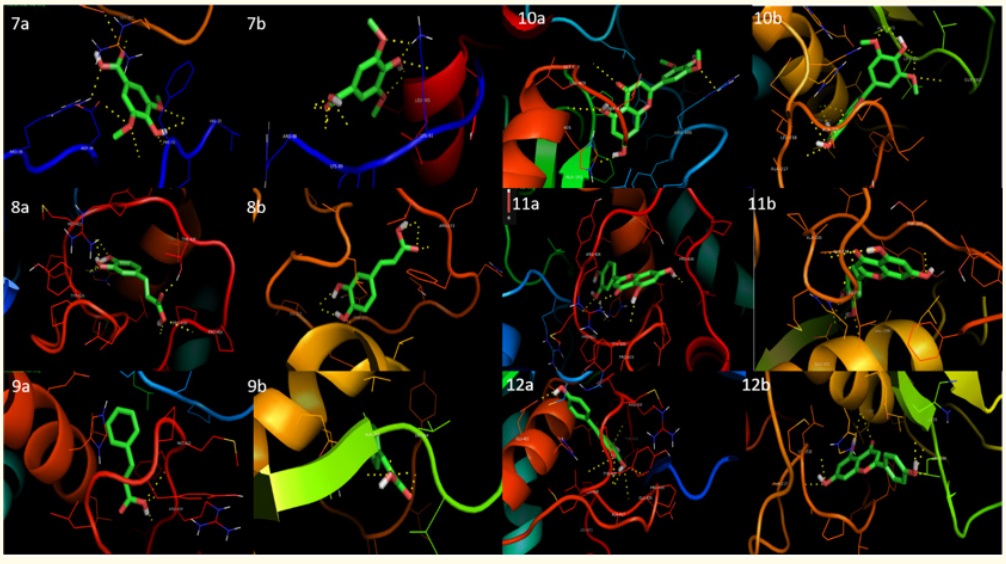


Figure 2: *Docking conformations of a) MMP9 b) MMP2 with 7. Syringic acid 8. Caffeic acid 9. Cinnamic acid 10. Tricin 11. Luteolin 12. Apigenin.*

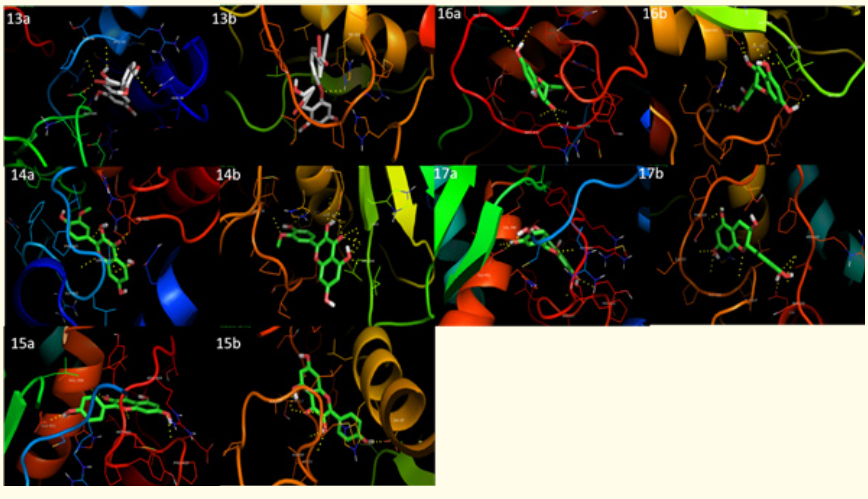


Figure 3: *Docking conformations of a) MMP9 b) MMP2 with 13. Quercetin 14. Isorhamnetin 15. Kaempferol 16. Catechin 17. Epicatechin.*

Discussion

Ischemic brain injury or cerebral ischemia, a prominent death cause around the globe, is a result of insufficient or obstructed blood supply to brain [2]. Blood brain barrier is a major protective layer around the brain and is composed of layers of endothelial cells, basal lamina, pericytes and astrocytic end feet [4,5]. The gaps between the endothelial cells are filled by the tight junction proteins like occludin, claudin-5 and ZO-1 which act as main barrier between blood and brain structurally [49,50]. The major constituents of basal lamina are type IV collagen, heparin, laminin and fibronectin [10-12]. The zinc dependent endopeptidases, the matrix metalloproteinases, have

significant role in extracellular matrix remodelling and are effective in breakdown of collagen IV, fibronectin, occludin and claudin-5 [11,12,51]. In ischemic state, hypoxic conditions and oxidative stress prevails which results in high levels of MMP2 and MMP9. These high levels of MMPs are responsible for the disruption of blood brain barrier as they are capable of degrading type IV collagen and fibronectin of basal lamina and occludin and claudin-5 of endothelial layers [51]. Hence, such increase in levels of MMPs and thus blood brain barrier disruption in ischemic brain results in blood brain barrier leakage, edema, haemorrhagic transformation, infiltration of leukocyte and progression of inflammation [2,52]. Many researches in this concern made it evident that inhibition of these MMPs may be an effective treatment for cerebral ischemia [10,11,12,52]. Many treatments are still in clinical trials but very few are in application, but they also pose many side effects [10,11,16,17]. Treatment through dietary compounds may have no or least side effects and also these compounds will be easy to deliver through diet [9,34-36,53,54]. Rice a staple crop, has majority of its constituents having high antioxidant and anti-inflammatory properties which may be of great support for treating oxidative stress and inflammation in ischemic brain [19,34-36,38]. Analysis of 35 rice constituents on the basis of the physiochemical properties (Table 2 and 3), bioactivity scores (Table 4) and ADMET properties (Table 5-10) for detecting their efficacy as brain targeted drug gave 17 constituents (Ferulic acid, p-Coumaric acid, Sinapic acid, Protocatechuic acid, p-hydroxy benzoic acid, Vanillic acid, Syringic acid, Caffeic acid, Cinnamic acid, Tricin, Luteolin, Apigenin, Quercetin, Isorhamnetin, Kaempferol, Catechin and Epicatechin). MMP2 and MMP9 being the most well-established targets of cerebral ischemia, were docked with the above selected 17 constituents and resulted in high negative binding energies providing strong evidence for effective structural inhibition of targets by the compounds *in-silico* (Table 11) [10-17,34]. Bhattacharya., *et al.* in their study of molecular docking on MMP2 and MMP9 inhibition with piroxicam for treating cerebral ischemia reported binding energies of -9.75 kcal/mol for MMP2 and -6.47 kcal/mol for MMP9 which are comparable with our results as majority of docked complexes have binding energies in the range of -6 to -9kcal/mol. But as piroxicam is a NSAID this may have many side effects which prove our approach of treating cerebral ischemia with rice constituents a more effective one [10]. In a past study by Pandey., *et al.* molecular docking of MMP2 and MMP9 with quercetin showed similar high negative binding energies thus acting as a support to our results [55]. Li., *et al.* in their *in vitro* inhibition study of MMP2 and MMP9 by myricetin and kaempferol proved that they are effective inhibitors of MMPs and are capable to reduce the levels of MMPs. The hydroxyl group of both these inhibitors was reported to have effective interaction with the target proteins thus providing strength to our analysis [56]. Another study by Ahmad., *et al.* for inhibition of MMP2 by a curcumin analog difluorinated benzylidene gave negative binding energy of -6.39 kcal/mol which is less than the binding energies of complexes formed by majority of rice constituents proving that rice constituents may act as better inhibitors for target MMPs [57]. Hence, on the basis of rice constituents docking analysis it is concluded that apigenin, quercetin, kaempferol, and epicatechin may have the greatest inhibitory potential for the considered effective targets. The binding energy of apigenin with MMP9 and MMP2 are -9.11 and -9.15 kcal/mol respectively proving that apigenin may have highest inhibition potential to work as a leading drug for the purpose out of all the rice constituents considered. Then quercetin, with binding energies of -8.1 kcal/mol and -8.07 kcal/mol for MMP9 and MMP2 respectively showed efficient inhibition, which is an already reported compound for MMP2 and MMP9 inhibition and is an essential part of antioxidant composition of rice. Kaempferol complex with MMP9 and MMP2 gave binding energies of -8.05 and -8.84 kcal/mol respectively thus providing effective evidence of its high inhibition capability for both considered MMPs. Catechin and epicatechin showed exclusively high binding energies of -9.08 and -9.17 kcal/mol for MMP2 but the binding energy with MMP9 was comparable to other compounds.

Henceforward, rice with its great nutraceutical property may be a highly effective source of MMP inhibitors and may be considered as an effective weapon to fight against cerebral ischemia. Thus, our hypothesis of treating cerebral ischemia with rice constituent stands in great demand for further research to find a persuasive treatment for the same.

Conclusion

Present study focuses on the treatment of cerebral ischemia by structural inhibition of MMPs to reduce the BBB disruption in diseased state by rice constituents along with reducing oxidative stress and inflammation. 17 constituent compounds of rice were analysed by molecular docking with MMP2 and MMP9 for estimating the effectiveness of inhibition. Majority of compounds were found to have high

negative binding energies showing highly significant inhibition proving rice as an eminent source of treatment for cerebral ischemia. In concluding remarks this study suggests that rice constituents being dietary compounds may work as effective inhibitors of MMPs with no side effects and may be a highly potent treatment for cerebral ischemia therefore extensive research is needed in this context to protect the world from the vulnerability of such a deadly disease.

Conflict of Interest

There is no conflict of interest between authors.

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