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Docking & Virtual Screening of Edible Mushroom Derived Compounds as *Plasmodium falciparum* Triosephosphate Isomerase-Phosphoglycolate Inhibitor

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ABSTRACT: Purpose: The development of resistance by the parasite against the available anti-malarial drugs has underscored the importance to develop a new drug targets and pharmacophores to treat the disease with less adverse effects. *Plasmodium falciparum* Dehydrofolate reductase/ Thymidylate Synthatase (*pf*DHFR-TS), *Pf* Triosephospate isomerase (*pf*TIM/PfTPI) and Translationally controlled tumor Protein (TCTP) of *Plasmodium falciparum* are established target of many anti malarial drug. Novel chemical entities that exhibit new mechanisms of antiplasmodial action are needed. Herein, we presented an in-silico study of few compounds derived from edible mushroom as anti- malarial agent. **Methods:** In this present study, virtual Screening and docking simulation was performed to investigate the binding mode of 13 edible mushroom derived compounds with *Wild-type Plasmodium falciparum dihydrofolate reductase-thymidylate synthase (PfDHFR-TS) complexed with WR99210, NADPH, and dUMP*. **Results:** The docking and ADME results 1,2 dihydroxymintlactone, D eritadenine, Tetrahydrobenzofuran, Cordycepin, Flammulinol , Lovastatin and Hericene showed significant results in terms of energy and ligand properties study. **Conclusion:** Mushroom derived compounds viz. *Cordycepin* and *Tetrahydrobenzofuran* reported from *Cordyceps melitaris* and *Lentinus squarrosulus*, edible non-toxic species has shown novel binding with the receptor model would be valuable starting point to develop anti-cancer therapeutics from mushroom.

KEYWORDS: *Plasmodium falciparum*; Virtual Screening; Docking; ADME.

INTRODUCTION

Malaria is one of the worlds most deadly disease cause by protozoa belongs to genus *Plasmodium*. The malaria parasite transmitted female Anopheles species mosquitoes (Cox, 2010). In South-East Asian region, India contribute about 70% malaria of cases and annually reports about two million cases and 1000 deaths (Dash, et al., 2008). The emergence of malaria parasite is great challenge to combating malaria (White, 2004). *Plasmodium falciparum (pf)* Dehydrofolate reductase/ Thymidylate Synthatase (*pfDHFR*-TS), *Pf* Triosephospate isomerase (*pf*TIM/PfTPI) and Translationally controlled tumor Protein (TCTP) were appropriate and effective target of existing anti-malarial drug reported till date. These receptors have shown frequent mutation leading to drug resistance malaria. Edible Mushroom has great medicinal

value (Guillamon, et al., 2010). Since longtime, different species of mushroom were used traditionally for the treatment of disease like Cancer, Microbial Infection etc(Das, et al., 2010). The North East India is a ideal habitat of Mushroom and reported their use as herbal medicine . Till date, many active phytochemicals has been characterized from different species of Mushroom by many authors. Some of the species included from this study are viz. *Cordyceps melitaris(Das, et al., 2010)* , *Flammulina velutipes*, *Grifola gargol*, *Hericium rinaceum (Kim, et al., 2011)*, *Leccinum extremioientale*, *Lentinus edods (Gunawardena, et al., 2014)*, *Pleurotus ostreatus (Schillaci, et al., 2013)* and *Lentinus squarrosulus.* The virtual screening and docking of Phytochemical with established biological target is a novel approach of selection of drug candidate (Gogoi, et al., 2012). In this study 13 mushroom compounds has been studies for their suitable binding with novel receptor. Bioinformatics studies have emerged as new techniques to investigate diseases at molecular level using *in silico* approaches. Thus, our aim was to carry out the molecular docking analysis to find out the inhibitory effect of secondary metabolites of 13 edible mushroom derived compounds on *pf*DHFR-TS receptor model.

MATERIALS & METHODS

Receptor Model Preparation

The three-dimensional crystal structure of *Plasmodium falciparum* Triosephospate isomerase (*pf*TIM/PfTPI) (PDB ID: 1LZO) (Parthasarathy, et al., 2002)was retrieved from PDB (http://www.rcsb.org/) and the structure was optimized using Molsoft Browser. The water molecules and co-crystallized ligands were removed before imported to Docking workspace.

Retrieval of Mushroom Derived Compounds

In this research investigation, 13 mushroom derived compounds were studied (Shown in Table-2). These compounds were reported from viz. *Cordyceps melitaris*, *Flammulina velutipes*, *Grifola gargol*, *Hericium erinaceum*, *Leccinum extremioientale*, *Lentinus edods*, *Pleurotus ostreatus* and *Lentinus squarrosulus species of edible mushroom native to North-east India*. *Compound were sketched using Marvin tool and optimized at* Chem-BioDraw Ultra 12.0 (Strack, 2001).

Physiochemical Properties calculation and PASS Prediction

The physiochemical property calculation is an *in silico* screening technique that is designed to decrease the load on the actual number of wet-lab experiments to be conducted. In this calculation the compounds violating lipinski's rule of 5, LEAD, MDDR, WDI drug like rule were predicted (Norinder and Bergstrom, 2006). Compounds are optimized using force field or energy minimization by using the software ChemBio 3D Ultra 12.0 .Then the best compounds with minimum total energy are selected by comparing with the minimum total energy of the drugs . The Prediction of Activity Spectra for substances was predicted using PASS software (Lagunin, et al., 2000).

Docking Studies

The Molecular Docking was performed in Autodock 4.0 and Molegro Virtual Docker software(Thomsen and Christensen, 2006). Molegro Virtual Docker (MVD) (Molegro APS: MVD 5.0). MVD is molecular visualization and molecular docking software which is based on a differential evolution algorithm; the solution of the algorithm takes into account the sum of the intermolecular interaction energy between the ligands and the protein and the intermolecular interaction energy of the ligand. The docking energy scoring function is based on the modified piecewise linear potential (PLP) with new hydrogen bonding and electrostatic terms included. The bonds flexibility of the ligands was set and the side chain flexibility of the amino acids in the binding cavity was set with a tolerance of 1.10 and strength of 0.90 for docking simulations. RMSD threshold for multiple cluster poses was set at <2.00 Å. The docking algorithm was set at a maximum iteration of 1500 with a simplex evolution size of 50 and a minimum of 20 runs (Thomsen and Christensen, 2006)..

ADME Prediction

The ADME (Absorption, Distribution, Metabolism and Excretion of Molecules) properties were predicted using PreADMET (www.preadmet.bmdrc.org) server to know whether the compounds have the potential of adverse effect in human (Norinder and Bergstrom, 2006). Mushroom compound ADME properties has been presented at Table-5.

RESULTS & DISCUSSION

Prediction of Physiochemical Property, ADME Study and Docking of 13 mushroom compound (Table 1 and 2) was performed and around 80% of molecules are supporting all the drug-like properties. The physiochemical properties such as Logp , Number of hydrogen bond etc were predicted as shown in the Table 3 and observed that all the compounds are qualifying the Lipinski's rule of five(Lipinski, et al., 2001). The prediction of Force filed were predicted and Energy value was scored on the basis of Kcal/mol (Table-4) . In PreADMET server CMC, Lead like, MDDR and WDI rule are predicted and more than 50% compounds not violate these rules (Table-6). The Docking investigation clearly reflected the good binding of 1,2 dihydroxymintlactone, Leccinine, Tetrahydrobenzofuran and D-arabinitlo estar with the receptor (Table-7). The ADME results of these compounds has showed optimum scores i.e. Human Intestinal Absorption, CcCo-2 permeability, MDCK permeability, Skin permeability Plasma Protein binding and Blood Brain penetration were showed the novelty of these mushroom derived compound as a candidate drug. The Hydrogen bonding (>3.5 Å) of few compounds such as 1,2 dihydroxymintlactone, D eritadenine, Tetrahydrobenzofuran, Cordycepin, Flammulinol , Lovastatin and Hericene are promiseing very promising.

Table 1 The Compounds.

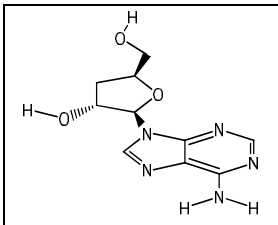
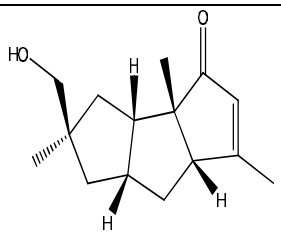
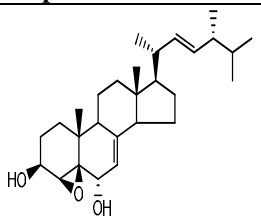
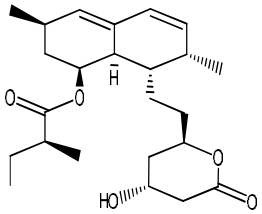
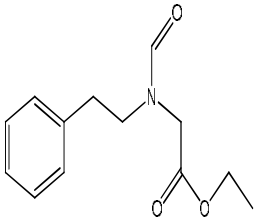
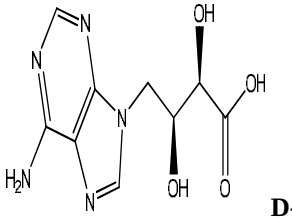
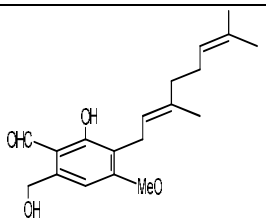
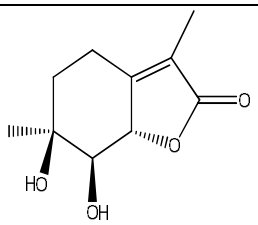
 **Cordycepin (*Cordyceps melitaris*)**	 **Flammulinol A (*Flammulina velutipes*)**	 **Gargalol A (*Grifola gargol*)**	 **Lovastatine (*Pleurotus ostreatus*)**
 **Leccinine (*Leccinum extremioientale*)**	 **D-Eritadenine (*Lentinus edods*)**	 **Hericene A (*Hericium erinaceum*)**	 **1,2 dihydroxymintlactone (*Lentinus squarrosulus*)**

Table 2 Compounds format conversion format.

SL NO	COMPOUND NAME	IUPAC NAME	CHEMICAL FORMULA	SMILES
1	Cordycepin (*Cordyceps melitaris*)	(2R,3R,5S)-2-(6-amino-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3-ol	C10H13N5O3	O=C(C=C1C)[C@]2(C)[C@@]1([H])C[C@]3([H])C[C@](CO)(C)C[C@]23[H]
2	Flammulinol A (*Flammulina velutipes*)	(2R,3aS,3bS,6aS,7aR)-2-(hydroxymethyl)-2,3b,6-trimethyl-3,3a,3b,6a,7,7a-hexahydro-1H-cyclopenta[a]pentalen-4(2H)-one	C15H22O2	C[C@]12CC[C@H](O)[C@H]3[C@@]1(O3)[C@@H](O)C=C4C5[C@]([C@@H]([C@H](C)/C=C/[C@H](C)C(C)C)CC5)(C)CCC24
3	Gargalol A (5*Grifola g6argol*)	(1aS,2S,4aR,6aR,7R,11S,11aS)-7-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-4a,6a-dimethyl-1a,2,3,4,4a,4b,5,6,6a,7,8,9,9a,11-tetradecahydrocyclopenta[7,8]phenanthro[1,10a-b]oxirene-2,11-diol	C28H44O3	CCCCC/C=C\C/C=C\CCCCCCCC(OC[C@@](H])(O)[C@@](O)([H])[C@@](O)([H])CO)=O
4	D-arabinitol e8ster (*He9ricium erin10aceum*)	(9Z,12Z)-(2R,3R,4R)-2,3,4,5-tetrahydroxypentyl octadeca-9,12-dienoate	C23H42O6	C/C(C)=C/CC/C(C)=C/CC(C(O)=C(CN(CCC1=CC=CC=C1)C2=O)C2=C3)=C3OC
5	1a *(Hericium erinaceum)*	(E)-5-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one	C27H33NO3	C/C(C)=C/CC/C(C)=C/CC(C(O)=C(CNC1=O)C1=C2)=C2OC

6	1b (*Hericium erinaceum*)	(E)-5-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxyisoindolin-1-one	C19H25NO3	C/C(C)=C/CC/C(C)=C/CC1=C(OC)C=C(COC(CCCCCCCCCCCCCCC)=O)C(C=O)=C1O
7	Hericene A *(Hericium erinaceum)*	(E)-4-(3,7-dimethylocta-2,6-dien-1-yl)-2-formyl-3-hydroxy-5-methoxybenzyl palmitate	C35H56O5	C/C(C)=C/CC/C(C)=C/CC1=C(OC)C=C(CO)C(C=O)=C1O
8	b *(Hericium erinaceum)*	(E)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-6-(hydroxymethyl)-4-methoxybenzaldehyde	C19H26O4	O=C(OCC)CN(C=O)CCC1=CC=CC=C1
9	Leccinine *(Leccinum extremioientale)*	ethyl 2-(N-phenethylformamido)acetate	C13H17NO3	NC1=NC=NC2=C1N=CN2C[C@@H]([C@H](C(O)=O)O)O
10	D-eritadenine *(Lentinus edods)*	(2R,3S)-4-(6-amino-9H-purin-9-yl)-2,3-dihydroxybutanoic acid	C9H11N5O4	O=C1C(C)=C2CC[C@@](O)(C)[C@H](O)[C@H]2O1
11	1,2 dihydroxymintl actone *(Lentinus squarrosulus)*	(6S,7R,7aS)-6,7-dihydroxy-3,6-dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one	C10H14O4	CC1=C(C(CC(C)C)=O)OC2=C1CC[C@@](O)(C)[C@@H]2O
12	Tetrahydrobenzofuran *(Lentinus squarrosulus)*	1-((6S,7S)-6,7-dihydroxy-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-3-methylbutan-1-one	C15H22O4	O[C@@H](C1)C[C@@H](CC[C@@H]([C@@H](C)C=CC2=C[C@H](C)C3)[C@@]2([H])[C@H]3OC([C@@H](C)CC)=O)OC1=O
13	Lovastatine *(Pleurotus ostreatus)*	(S)-(1S,3R,7S,8S,8aR)-8-(2-((2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2-methylbutanoate	C24H36O5	O=C(C=C1C)[C@]2(C)[C@@]1([H])C[C@]3([H])C[C@](CO)(C)C[C@]23[H]

Table 3 Physiochemical properties of mushroom derived compounds.

Sl N.	Compound	tPSA	nATOMS	MW	nON	nOHNH	nVIOLATION	nrotb	Vloume	Clopp
1	Cordycepin (*Cordyceps melitaris*)	119.3	18	251.246	8	4	0	2	210.487	1.15
2	Flammulinol A (*Flammulina velutipes*)	37.299	17	234.339	2	1	0	1	234.908	2.35
3	Gargalol A (*Grifola gargol*)	52.984	31	428.657	3	2	1	4	439.417	5.4
4	D-arabinitol ester (*Hericium erinaceum*)	107.217	29	414.583	6	4	0	20	429.777	4.1
5	Hericene A *(Hericium erinaceum)*	72.838	40	556.828	5	1	2	24	588.069	10.12

6	b *(Hericium erinaceum)*	66.761	23	318.413	4	2	0	8	316.332	3.81
7	Leccinine *(Leccinum extremioientale)*	46.614	17	235.283	4	0	0	7	227.547	1.28
8	D-eritadenine *(Lentinus edods)*	147.388	18	253.218	9	5	0	4	205.716	-1.86
9	1,2 dihydroxymintlactone *(Lentinus squarrosulus)*	66.761	14	198.218	4	2	0	0	179.257	-0.22
10	Tetrahydrobenzofuran *(Lentinus squarrosulus)*	70.667	19	266.337	4	2	0	3	256.597	1.39
11	Lovastatine *(Pleurotus ostreatus)*	72.838	29	404.547	5	1	0	7	400.574	3.68

Table 4 Energy Optimization result of mushroom compounds.

S N.	**COMPOUND NAME WITH (SPECIES NAME)**	**STRETCH**	**BEND**	**STRETCH-BEND**	**TORSION**	**NON-1, 4 VDW**	**1,4 VDW**	**DIPOLE/ DIPOLE**	**TOTAL ENERGY (kcal/mol)**
1	Cordycepin *(Cordyceps melitaris)*	0.945	22.515	-0.0218	7.473	5.089	13.399	0.837	40.059
2	Flammulinol A *(Flammulina velutipes)*	1.277	9.319	-0.040	16.794	-5.327	8.092	-1.348	28.766
3	Gargalol A *(Grifola gargol)*	12.843	37.864	0.474	35.558	-8.907	23.512	-2.308	99.036
4	D-arabinitol ester *(Hericium erinaceum)*	1.654	8.451	0.664	2.070	-9.836	20.600	-4.682	18.922
5	1a (*Hericium erinaceum)*	1.853	16.691	0.046	-10.582	-7.588	20.689	-7.224	13.885
6	1b (*Hericium erinaceum)*	1.578	14.358	0.017	-4.448	-5.015	10.303	-6.455	10.339
7	Hericene A (*Hericium erinaceum)*	3.718	15.398	0.791	-9.061	-1.121	28.568	3.878	42.170

Table 5 ADME properties of compounds.

SL NO	COMPOUND NAME	ABSORPTION				DISTRIBUTION	
		HUMAN INTESTINAL ABSORPTION (HIA, %)	CaCo-2 PERMIABILITY (nm/sec)	MDCK PERMIABILITY (nm/sec)	SKIN PERMIABILITY (logKp, cm/hour)	PLASMA PROTIEN BINDING(%)	BLOOD BRAIN BARRIER PENITRATION (C.brain/C.blood)
1	*Cordycepin (Cordyceps melitaris)*	72.098	0.208	0.721	-5.137	8.828	0.083
2	Flammulinol A (*Flammulina velutipes*)	95.185	11.440	101.636	-2.540	92.217	1.891
3	Gargalol A (Grifola gargol)	94.208	40.878	1.997	-1.379	100	8.147
4	D-arabinitol ester (*Hericium erinaceum*)	81.547	20.180	81.228	-1.428	100	2.193
5	Hericene A	96.652	48.77	37.677	-0.770	100	13.101
6	Leccinine (*Leccinum extremioientale*)	98.026	21.790	222.62	-2.483	72.359	0.052
7	D-eritadenine (*Lentinus edods*)	34.876	0.678	0.854	-5.058	8.898	0.049
8	1,2 dihydroxymintlactone (*Lentinus squarrosulus)*	84.159	18.952	5.903	-4.362	36.493	0.427

Table 6 Drug likeness prediction using PreADMET Server.

SL NO.	COMPOUND NAME	CMC LIKE RULE VIOLATION	LEAD LIKE RULE VIOLATION	MDDR LIKE RULE VIOLATION	LIPINSKI RULE OF FIVE VIOLATION	WDI LIKE RULE VIOLATION
1	**Cordycepin** *(Cordyceps melitaris)*	-	-	-	+	+
2	**Flammulinol A** *(Flammulina velutipes)*	+	+	-	+	+
3	**Gargalol A** *(Grifola gargol)*	-	**-(2)**	_	_	**_(8)**
4	**D-arabinitol ester** *(Hericium erinaceum)*	-	**-(2)**	**-(2)**	+	**-(5)**
5	**b** *(Hericium erinaceum)*	+	-	**-(2)**	+	+
6	**Leccinine** *(Leccinum extremioientale*)	+	+	**-(2)**	+	+

10	**D-eritadenine** (*Lentinus edods*)	-	-	**-(2)**	+	+
11	**1,2 dihydroxymintlactone** *(Lentinus squarrosulus)*	+	-	**-(2)**	+	+
12	**Tetrahydrobenzofuran** (*Lentinus squarrosulus)*	+	+	**-(2)**	+	+
13	**Lovastatine** (*Pleurotus ostreatus)*	+	**-(2)**	_	+	+

NB: Plus sign indicate number of Violation of drug like properties.

Table 7 Docking Scores

Sl No.	Ligand	Rerank Score	HBond
1	D-arabinitlo estar	-75	-9.57561
2	Leccinine	-73	-4.98611
3	1,2 dihydroxymintlactone	-69	-9.57923
4	Tetrahydrobenzofuran	-69	-9.99647

Table 8 Prediction interactions

	LIGAND				PROTEIN			
SL NO	COMPOUND	ATOM_ID	ELEMENT	ANNOTATED DISTANCE	Internal Residue	Atom_id	Residue	Element
1	D-arabinitlo estar	24	O	3.11 Å	9	182	Lys12	H
		25	O	1.95 Å	9	180	Lys12	H
		27	O	3.47 Å	9	181	Lys12	H
		30	O	2.35 Å	9	180	Lys12	H
2	Leccinine	12	O	3.34 Å	9	181	Lys12	H
		11	O	2.30 Å	9	180	Lys12	H
3	1,2 dihydroxymintlactone	7	O	2.52 Å	209	3364	val 212	H
		7	O	2.33 Å	229	3659	Gly232	H
		9	O	2.09 Å	209	3364	val 212	H
		9	O	1.51 Å	229	3659	Gly232	H
		19	H	3.43 Å	208	3351	Ser211	O
		20	H	3.05 Å	208	3351	Ser211	O
4	D eritadenine	19	H	3.46 Å	206	3353	Gly209	O
		18	H	2.31 Å	227	3623	Leu230	O
		20	H	2.33 Å	162	2626	Glu165	O
		23	H	2.32 Å	227	3623	Leu230	O
		9	N	2.77 Å	9	169	Lys12	H
		26	H	3.61 Å	207	3342	Gly210	O
		27	H	2.43 Å	9	169	Lys12	N
		16	O	2.71 Å	208	3353	Ser211	H
		17	O	2.60 Å	230	3670	Asn233	H
5	Tetrahydrobenzofuran	15	O	1.67 Å	9	180	Lys12	H
		31	H	3.32 Å	94	1488	Glu97	O
6	cordycepin	0	N	3.15 Å	208	3356	Ser211	H
		6	N	2.64 Å	230	3670	Asn233	H
		6	N	2.37 Å	231	3681	Ala 234	H
		8	N	2.72 Å	230	3670	Asn233	H

		16	H	2.34 Å	207	3342	Gly 210	O
		15	O	2.52 Å	209	3364	val 212	H
		15	O	2.32 Å	229	3659	Gly232	H
7	Flammulinol a	11	O	2.46 Å	231	3681	Ala 234	H
		19	O	1.97 Å	229	3659	Gly232	H
		19	O	2.40 Å	229	3659	Gly232	H
		25	H	3.25 Å	209	3360	val 212	O
		21	O	2.38 Å	209	3364	val 212	H
		21	O	1.31 Å	229	3659	Gly232	H
		41	H	3.01 Å	208	3351	Ser211	O
		19	O	3.53 Å	208	3357	Ser211	H
8	Lovastatin	2	O	1.60 Å	9	180	Lys12	H
9	Hericene a	39	O	3.34 Å	9	181	Lys12	H
		38	O	2.23 Å	229	3659	Gly 232	H
		38	O	2.12 Å	209	3364	val 212	H
		59	H	2.69 Å	227	3623	Leu230	O
		59	H	2.49 Å	207	3342	Gly 210	O
		16	O	2.88 Å	229	3659	Gly232	H
10	Gagalol A	38	H	3.50 Å	206	3335	Gly209	O

Since these compounds reported from edible mushroom . Therefore there is lots of scope to continue further research in this aspect.

CONCLUSION

The Compound 1,2 dihydroxymintlactone, D eritadenine, Tetrahydrobenzofuran, cordycepin, Flammulinol , Lovastatin and Hericene has followed all the rule and regulation necessary for a ideal drug candidate. The Docking Result and ADME score of these compounds are very interesting. Therefore further malarial *in vitro* test may be performed for these law molecule weight active compounds.

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