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Osteosarcoma's STAT-3 Vrs *Kaempferia parviflora's* Compounds : Possible Drug Candidates

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ABSTRACT

Osteosarcoma is a dominant type of bone cancer, associated with osteophytes (bone cells). Afflicts all age groups; generally manifesting in long bones of human physiology(also other parts; including fine joints). Chemotherapy, surgery and radiation are the current therapeutics – with uncertain results; often associated with high degree of failure; swift relapse; rebound aggression and above all with debilitating post treatment out come conditions. In this investigation in silico drug designing procedures have been used to predict natural compounds from *Kaempferia parviflora* (black ginger) as possible drug candidates for osteosarcoma. 8 of its phyto-compounds (PCs) are found to be non-toxic and also pass the Lipinski's rule of 5 (@ 100%) vis-à-vis the over expressed Signal Transducer And Activator Of Transcription 3(STAT3) protein of the dreaded osteosarcoma. All the 8 PCs indicate better binding affinity (greater likeness) than the current best popular allopathic drug Zoledronic acid (Toxic). All the 8 offer good-excellent likeness. Alpha- Copaene (non Toxic) emerges as the Champion.

Keywords: Phytochemicals, STAT3, bone cancer, Sarcoma, In silico, molecular docking.

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Introduction

One of the unusual types of cancer is osteosarcoma i.e., fleshy growth [1,2] i.e., cancer of the bones & joints. Not all osteosarcomas are cancers; most being benign; invariably painful; paralyzing and finally fatal. Its genesis is thought to have a nexus with genetic and environmental factors. It originates from mesenchyma (connective tissues). The tumor cells produce immature osteoid/s arising from the osteoblast (bone formation systhesiser) and is limited only to the osteological frame hence Osteosarcoma. Pan globally quite wide spread indeed among all the human races [3], is more common among children, young adults and in elderly persons [4]; primarily due anabolic condition (our view point). Patients of Osteosarcoma are increasing at rapid rate today in the world. Males are more affected than females; Statistics Report [5]. The osteosarcoma patients have common symptoms of pain in bone, tender mass and hyper vascularity [6]. Imaging studies and radiographs are used to detect the regions of osteosarcoma. It is common in long bones viz., femur. It is diagnosed by fine needle aspirates in patients. The treatments option for Osteosarcoma is neoadjuvant therapy followed by surgical resection and adjuvant chemotherapy which leads a successful curing of this disease [7].

Animals also suffer from Sarcomas. This communication is limited to human Osteo-Sarcoma. The oldest being dated to 1.7-2 million years before present [8]. In present times the ever present & essential; versatile transcription protein namely 'Signal Transducer and Activator of Transcription 3' (STAT3) is found in human osteosarcoma cell line samples. The frequent presence of STAT3 in osteosarcoma represents that, over expression of STAT3 protein in human body leads to Osteosarcoma [9]. In this in silico investigation STAT3 protein is taken as the target and never before used novel natural compounds as the possible candidates for drug likeness.

India is the land of medicinal plants due to her unique agro-meteorology & geo-topology well defined in her National School Of Medicine i.e., Ayurveda (2nd Millennia BC). Among the various medicinal plants of India *Kaempferia parviflora*is (Black ginger) is reported to be full of medicinal properties and is well described in the Ayurvedic literatures (collateral info). It is also native to South-East Asia, India and Thailand [10]. Its medicinal properties containing formulations &extracts has and is being used for antiallergenic,anti-inflammatory, anti-mutagenic, anti-depressive, anti-cholinesterase, anti-microbial, anti-cancer, anti–-peptic ulcer, cardioprotective, anti-obesity and aphrodisiac [11]. However, *Kaempferia parviflora* has numerous phyto-compounds (PC) and some have less efficacy while others may be inhibitive. There is also no reference about its use in Bone & Joint cancers or in on-bone fleshy mass growth management. Hence, we have targeted the phyto-compounds of *Kaempferia parviflora*is against STAT3 protein of Osteosarcoma to predict which of the constituent compounds offers 'more likeness' and posits well as (natural) drug candidate sources. 1st Ground breaking study. Thus, is not exhaustive.

Material and method

Gene target selection of osteosarcoma

STAT3 protein (gene name) is frequently identified in osteosarcoma cell line. Search in UniProt database [12] indicates its entry id as P40763, of 770 base pairs length, mass 88,068 Da., and the best option human sourced protein X-ray crystallography structure is obtained from PDB Id 6NJS at a resolution of 2.70 Å from PDB database along with nucleic acids [13]. This is the targeted protein selected for this in silico investigation. The 3D-structure of the STAT3 protein was viewed under Discovery studio visualizer version 2019 [14]. And, chain A of the structure was selected for the study.

Prediction of binding sites of the STAT3 protein

Binding sites of a protein defines the active sites of the molecules, where the small molecules will get attached. Thus, CastP webserver [15] has

been used for prediction the binding sites of STAT3.

Reported PCs from *Kaempferia parviflora* (black ginger)

Kaempferia parviflora has various medicinal properties associated with numerous phyto compounds (PCs). For such objectives, PubChem database has been used [16].

Lipinski rule of five – Ro5

The RO5 [17] states that (in in silico studies) any oral active drug should satisfy the rules such as Molecular mass (<=500 D), logP(<=5), Hydrogen bond donor(<=5), Hydrogen bond acceptors(<=10), Molar refractivity (40-130). This is the primary selection criteria. Violation of any one of the rules disqualifies the candidate compound as a potential source. TargetNet web server [18] has been used to predict the RO5 for all the phytochemicals taken for the study (http://targetnet.scbdd.com/calcnet/calc_rule_text/#). In order to check the toxic nature of the compounds that pass through the RO5, Protox-II server [19] and Toxicity checkerserver under mculeenvironment [20] tools have used.

Molecular docking study of selected compounds from *Kaempferia parviflora* against STAT3 protein of osteosarcoma.

The compounds from *Kaempferia parviflora* follow the RO5 and found non-toxic in nature were further processed for the molecular docking study against the STAT3 protein. In order to perform molecular docking study a widely accepted software namely Autodock 4.2 tool [21] has been used in the investigation to check efficiencies of ligands selected for study. The best-docked complexes were characterized and processed for further computational analysis based on binding energy values, ligand efficiency, inhibition constant and intermolecular hydrogen (H)-bonds. Here in the investigation a widely used drug in osteosarcoma namely Zoledronic Acid (Za) [22] taken for the comparative study against the STAT3 protein.

Results

Selected gene

In the investigation on osteosarcoma, it was found that, the protein STAT3 is highly expressed in this disease. The details of this protein are obtained from UniProtdatabase. The 3D-structure of STAT3 protein is obtained from PDB database with PDB Id 6NJS, Here the chain A of the structure selected for the study.

Binding sites of STAT3 protein

Using the CastPserver, the active sites of the STAT3 protein obtained. The predicted binding of STAT3 protein is THR236, ASP237, LEU240, ALA241, TRP243, LYS244, ARG245, GLN248, LYS318, SER319, PHE321, VAL322, VAL323, GLN326, GLU455, THR456, HIS457, SER458, LEU459, ASN485, PRO487 and LYS488. These are the obtained binding sites of STAT3 protein.

PCs of *Kaempferia parviflora*

Black ginger is a medicinal tuber\rhizome. Its medicinal properties yet to be discovered in wide range. In the current study, the reported PCs from black ginger is obtained from various research papers. Table 1 presenting 42 PCs obtained from various literature papers [23,24,25]. The details of the PCs are found from PubChem database.

Lipinsk's rule of 5 and Toxicity

The Rule of 5 of Lipinski plays an important role in drug discovery. This rule is widely used to check whether the compounds (are likely to) exhibit\follow the desired pharmacokinetic properties so as to merit as likely candidates for orally active systemic (suitable) drug for the human physiology. Hence, Lipinsk's 5 has assumed vital importance. It also includes the ADME (Absorption, Distribution, Metabolism and Excretion) properties through its parametric distribution and mathematical evaluation. Black ginger has 42 PCs and all of these have been examined vis-à-vis Lipinsk's rule of 5 using TarGet Net server. The results are given in Table 2.

Finding: 14 PCs out 42 PCs do not follow the Lipinsk's rule of 5. Thus, these (1/3rd) compounds were discarded. The remaining 28 compounds (2/3rd) were been taken for toxicity

processing. Two web servers namely ProTox-II server and Toxicity checker tool have been used to check the toxicity of the PCs. Only 8 PCs of the black ginger qualified the servers tests. Table 3 presents the results. Only 8 PCs (<20%) of the42 PCs from the black ginger follow Lipinsk's rule of 5 and are also non-toxic.

Table 1: Description of Phytochemical compounds present in *Kaempferia parviflora*

SL. No.	Chemical name	Molecular formula	PMID	SMILE ID
1.	5,7 - dimethoxyflavone	$C_{17}H_{14}O_4$	88881	COC1=CC2=C(C(=C1)OC)C(=O)C=C(O2)C3=CC=CC=C3
2.	5,7,4′ - trimethoxyflavone	$C_{18}H_{16}O_7$	44258616	COC1=C(C=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C=C3OC)OC)O)O
3.	3,5,7,3′,4′ - pentamethoxyflavone	$C_{20}H_{20}O_7$	97332	COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(O2)C=C(C=C3OC)OC)OC)OC
4.	Alpha-pinene	$C_{10}H_{16}$	6654	CC1=CCC2CC1C2(C)C
5.	Camphene	$C_{10}H_{16}$	6616	CC1(C2CCC(C2)C1=C)C
6.	beta-Pinene	$C_{10}H_{16}$	14896	CC1(C2CCC(=C)C1C2)C
7.	Limonene	$C_{10}H_{16}$	22311	CC1=CCC(CC1)C(=C)C
8.	Linalool	$C_{10}H_{18}O$	6549	CC(=CCCC(C)(C=C)O)C
9.	Borneol	$C_{10}H_{18}O$	64685	CC1(C2CCC1(C(C2)O)C)C
10.	Bornyl acetate	$C_{12}H_{20}O_2$	6448	CC(=O)OC1CC2CCC1(C2(C)C)C
11.	α-copaene	$C_{15}H_{24}$	442355	CC1=CCC2C3C1C2(CCC3C(C)C)C
12.	beta-Elemene	$C_{15}H_{24}$	6918391	CC(=C)C1CCC(C(C1)C(=C)C)(C)C=C
13.	(E) - caryophyllene	$C_{15}H_{24}O$	5352484	CC1=CCCC(=C)C2CC(C2CC1)(C)CO
14.	α-humulene	$C_{15}H_{24}O$	12445034	CC1=CCC(C=CC(C(=CCC1)C)O)(C)C
15.	Dauca - 5,8 - diene	$C_{15}H_{24}$	6429136	CC1=CCC2(CCC(C2=CC1)C(C)C)C
16.	gamma-Gurjunene	$C_{15}H_{24}$	90805	CC1CCC(C=C2C1CCC2C)C(=C)C
17.	beta-Selinene	$C_{15}H_{24}$	442393	CC(=C)C1CCC2(CCCC(=C)C2C1)C
18.	delta-Cadinene	$C_{15}H_{24}$	441005	CC1=CC2C(CCC(=C2CC1)C)C(C)C
19.	Spathulenol	$C_{15}H_{24}O$	92231	CC1(C2C1C3C(CCC3(C)O)C(=C)CC2)C
20.	Caryophyllene oxide	$C_{15}H_{24}O$	1742210	CC1(CC2C1CCC3(C(O3)CCC2=C)C)C
21.	Epi-α-muurolol	$C_{15}H_{26}O$	6429185	CC1=CC2C(CCC(C2CC1)(C)O)C(C)C
22.	α-cadinol	$C_{15}H_{26}O$	6431302	CC1=CC2C(CCC(C2CC1)(C)O)C(C)C
23.	Longiborneol acetate	$C_{17}H_{28}O_2$	91752502	CC(=O)OC1C2C3CCC1(C3(CCCC2(C)C)C)C
24.	lutein	$C_{40}H_{56}O_2$	5281243	CC1=C(C(CC(C1)O)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2C(=CC(CC2(C)C)O)C)C)C
25.	alpha-Carotene	$C_{40}H_{56}$	6419725	CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2C(=CCCC2(C)C)C)C)C
26.	neoxanthin	$C_{40}H_{56}O_4$	5281247	CC(=CC=CC=C(C)C=CC=C(C)C=C=C1C(CC(CC1(C)O)O)(C)C)C=CC=C(C)C=CC23C(CC(CC2(O3)C)O)(C)C
27.	beta-Carotene	$C_{40}H_{56}$	5280489	CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CCCC2(C)C)C)C)C
28.	Violaxanthin	$C_{40}H_{56}O_4$	448438	CC(=CC=CC=C(C)C=CC=C(C)C=CC12C(CC(CC1(O2)C)O)(C)C)C=CC=C(C)C=CC34C(CC(CC3(O4)C)O)(C)C
29.	Alpha-tocopherol	$C_{29}H_{50}O_2$	14985	CC1=C(C2=C(CCC(O2)(C)CCCC(C)CCCC(C)CCCC(C)C)C(=C1O)C)C
30.	alpha-Linolenic acid	$C_{18}H_{30}O_2$	5280934	CCC=CCC=CCC=CCCCCCCCC(=O)O
31.	Palmitic acid	$C_{16}H_{32}O_2$	985	CCCCCCCCCCCCCCCC(=O)O
32.	oleic acid	$C_{18}H_{34}O_2$	445639	CCCCCCCCC=CCCCCCCCC(=O)O
33.	palmitoleic acid	$C_{16}H_{30}O_2$	445638	CCCCCCC=CCCCCCCCC(=O)O
34.	tocopherols	$C_{28}H_{48}O_2$	14986	CC1=C(C=C2CCC(OC2=C1C)(C)CCCC(C)CCCC(C)CCCC(C)C)O
35.	Caffeic acid	$C_9H_8O_4$	689043	C1=CC(=C(C=C1C=CC(=O)O)O)O
36.	Vicenin-2	$C_{27}H_{30}O_{15}$	3084407	C1=CC(=CC=C1C2=CC(=O)C3=C(C(=C(C(=C3O2)C4C(C(C(C(O4)CO)O)O)O)O)C5C(C(C(C(O5)CO)O)O)O)O)O
37.	Ferulic acid	$C_{10}H_{10}O_4$	445858	COC1=C(C=CC(=C1)C=CC(=O)O)O
38.	Lumichrome	$C_{12}H_{10}N_4O_2$	5326566	CC1=CC2=C(C=C1C)N=C3C(=N2)C(=O)NC(=O)N3
39.	Cosmosiin	$C_{21}H_{20}O_{10}$	5280704	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)OC4C(C(C(C(O4)CO)O)O)O)O)O
40.	Narcissin	$C_{28}H_{32}O_{16}$	6223069	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)OC)O)O)O)O)O
41.	Isokaempferide	$C_{16}H_{12}O_6$	5280862	COC1=C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
42.	Undecanedioic acid	$C_{11}H_{20}O_4$	15816	C(CCCCC(=O)O)CCCCC(=O)O

Table 2:Lipinski's RO5 study was using TargetNet tool of phytocompounds of *Kaempferia parviflora*

SL. NO	PHYTOCOMPOUNDS	TPSA (Topological polar surface area) (<140)	MR (Molar Refractivity) (40-130)	MOLECULAR WEIGHT (<=500 D)	HBD-Hydrogen bond donor (<=5)	HBA1-Hydrogen bond acceptors (<=10)	LogP (<=5)	Lipinski rule of five
1.	**5,7-dimethoxyflavone**	48.67	80.904	282.29066	0.0	3.0	3.4772	100%
2.	**5,7,4′-trimethoxyflavone**	98.36	91.442	344.31544	2.0	6.0	2.897	100%
3.	**3,5,7,3′,4′-pentamethoxyflavone**	76.36	100.38	372.3686	0.0	6.0	3.503	100%
4.	**Alpha-pinene**	0.0	45.222	136.23404	0.0	0.0	2.9987	100%
5.	**Camphene**	0.0	45.222	136.23404	0.0	0.0	2.9987	100%
6.	**beta-Pinene**	0.0	45.222	136.23404	0.0	0.0	2.9987	100%
7.	**Limonene**	0.0	47.122	136.23404	0.0	0.0	3.3089	100%
8.	**Linalool**	20.23	50.4358	154.24932	1.0	1.0	2.6698	100%
9.	**Borneol**	20.23	46.5978	154.24932	1.0	1.0	2.1935	100%
10.	**Bornyl acetate**	26.3	56.335	196.286	0.0	2.0	2.7643	100%
11.	**α-copaene**	**0.0**	**67.143**	**204.35106**	**0.0**	**0.0**	**4.2709**	**100%**
12.	**beta-Elemene**	0.0	70.423	204.35106	0.0	0.0	4.7472	100%
13.	**(E)-caryophyllene**	20.23	69.9448	220.35046	1.0	1.0	3.6976	100%
14.	**α-humulene**	20.23	71.5848	220.35046	1.0	1.0	4.0062	100%
15.	**Dauca-5,8-diene**	0.0	68.783	204.35106	0.0	0.0	4.7252	100%
16.	**gamma-Gurjunene**	0.0	69.043	204.35106	0.0	0.0	4.5811	100%
17.	**beta-Selinene**	0.0	68.783	204.35106	0.0	0.0	4.7252	100%
18.	**delta-Cadinene**	0.0	69.043	204.35106	0.0	0.0	4.7252	100%
19.	**Spathulenol**	20.23	68.3428	220.35046	1.0	1.0	3.3858	100%
20.	**Caryophyllene oxide**	12.53	68.266	220.35046	0.0	1.0	3.9364	100%
21.	**Epi-α-muurolol**	20.23	70.7168	222.36634	1.0	1.0	3.7759	100%
22.	**α-cadinol**	20.23	70.7168	222.36634	1.0	1.0	3.7759	100%
23.	**Longiborneol acetate**	26.3	77.996	264.40302	0.0	2.0	4.1806	100%
24.	**lutein**	40.46	186.7556	568.87144	2.0	2.0	10.4033	50%
25.	**alpha-Carotene**	0.0	184.432	536.87264	0.0	0.0	12.4617	50%
26.	**neoxanthin**	73.22	186.6564	600.87024	3.0	4.0	8.7184	50%
27.	**beta-Carotene**	0.0	184.432	536.87264	0.0	0.0	12.6058	50%
28.	**Violaxanthin**	65.52	185.7976	600.87024	2.0	4.0	8.9698	50%
29.	**Alpha-tocopherol**	29.46	139.271	430.7061	1.0	2.0	8.8402	75%
30.	**alpha-Linolenic acid**	37.3	88.9898	278.4296	1.0	2.0	5.6605	75%
31.	**Palmitic acid**	37.3	80.7978	256.42408	1.0	2.0	5.5523	75%
32.	**oleic acid**	37.3	89.9378	282.46136	1.0	2.0	6.1085	75%
33.	**palmitoleic acid**	37.3	80.3238	254.4082	1.0	2.0	5.3283	75%
34.	**tocopherols**	29.46	134.305	416.67952	1.0	2.0	8.5318	75%
35.	**Caffeic acid**	77.76	47.1578	180.15742	3.0	4.0	1.1956	100%
36.	**Vicenin-2**	271.2	139.2274	594.5181	11.0	14.0	-2.3934	25%
37.	**Ferulic acid**	66.76	51.6268	194.184	2.0	4.0	1.4986	100%
38.	**Lumichrome**	91.5	68.2174	242.2334	2.0	4.0	0.7764	100%
39.	**Cosmosiin**	170.05	106.1112	432.3775	6.0	9.0	0.0499	75%
40.	**Narcissin**	258.43	145.8478	624.54408	9.0	15.0	-1.3841	25%
41.	**Isokaempferide**	100.13	80.481	300.26288	3.0	5.0	2.5854	100%
42	**Undecanedioic acid**	74.6	58.5346	216.2741	2.0	4.0	2.6665	100%
No. 24-34; 36; 39 & 40 Fail the Lipinski's Rule 5								

Table 3- Toxicity Checking the Phyto compounds *Kaempferia parviflora*

S.N.	Phytocompound	Tools	Toxic/Non-Toxic	PASS OR FAIL
1.	**5,7-dimethoxyflavone**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
2.	**5,7,4′-trimethoxyflavone**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
3.	**3,5,7,3′,4′-pentamethoxyflavone**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
4.	**Alpha-pinene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
5.	**Camphene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
6.	**beta-Pinene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
7.	**Limonene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
8.	**Linalool**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
9.	**Borneol**	Protox	**NON-TOXIC**	✓

		Toxicitychecker	**NON-TOXIC**	✓
10.	**Bornyl acetate**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
11.	**α-copaene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
12.	**beta-Elemene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
13.	**(E)-caryophyllene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
14.	**α-humulene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
15.	**Dauca-5,8-diene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
16.	**gamma-Gurjunene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
17.	**beta-Selinene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
18.	**delta-Cadinene**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
19.	**Spathulenol**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
20.	**Caryophyllene oxide**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
21.	**Epi-α-muurolol**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
22.	**α-cadinol**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
23.	**Longiborneol acetate**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
24.	**Caffeic acid**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
25.	**Ferulic acid**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
26.	**Lumichrome**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
27.	**Isokaempferide**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**NON-TOXIC**	✓
28.	**Undecanedioic acid**	Protox	**NON-TOXIC**	✓
		Toxicitychecker	**TOXIC**	✗
✗ **= Toxic**		✓ **= NON TOXIC**		

Molecular docking results of selected 8 compounds of black ginger and reported drug Zoledronic Acid against STAT3 protein of Osteosarcoma

The qualified8 PCs are as follows 5,7-dimethoxyflavone, Alpha-pinene, Borneol, α-copaene, Dauca-5,8-diene, delta-Cadinene, Epi-α-muurolol and α-cadinol. These PCs are further processed for molecular docking study using the Autodock 4.2 software. The grid box value taken for the study is for X-dimension = 66, Y-dimension = 76 and Z-dimension =70 with 0.375 Angstrom spacing.

For comparative study zoledronic acid (Za) - a reported drug of efficacy is taken andis also docked against the STAT3 protein of Osteosarcoma. Za has PubChem id of 68740 with molecular formula $C_5H_{10}N_2O_7P_2$ having smile id of C1=CN(C=N1)CC(O)(P(=O)(O)O)P(=O)(O)O. The 3D-structures of the 8 PCs of the black ginger and zoledronic acid have been downloaded from PubChem databsein SDF format. Thereafter

using the Biovia Discovery studio 2019 version, all the candidates were converted into.pdbformat and docked using Autodock 4.2 tool.

Table 4 shows the docking results of the 8 PCof the black ginger against STAT3 protein of human osteosarcoma.

Table 5 shows the results obtained from Protox server and Toxicity checker tool for Za It is found to be Toxic in nature.

Table 6 shows the docking results of Za against STAT3 protein of human osteosarcoma.

Table 4: Docking of screened Compounds from *Kaempferia parviflora* against STAT3 protein of osteosarcoma

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	α-copaene	-6.03	-0.38	37.96	1	GLN 248	2.03338
2.	delta-Cadinene	-5.78	-0.39	57.69	N/A	N/A	N/A
3.	Dauca-5,8-diene	-5.66	-0.38	71.13	N/A	N/A	N/A
4.	α-cadinol	-5.63	-0.35	74.45	3	LYS244,PHE321,THR456	2.509766667
5.	5,7-dimethoxyflavone	-5.3	-0.25	131.4	N/A	N/A	N/A
6.	Epi-α-muurolol	-5.0	-0.31	216.58	1	GLU455	1.83642
7.	Alpha-pinene	-4.43	-0.44	563.08	N/A	N/A	N/A
8.	Borneol	-4.21	-0.38	821.8	2	THR456,GLU455	2.46207

Table 5: Toxicity of Za

S.N.	Phytocompound	Tools	Toxic/Non-Toxic
1.	Zoledronic acid	Protox	NON-TOXIC
		Toxicitychecker	TOXIC

Table 6: Docking of Za *against STAT3* protein of Osteosarcoma

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Zoledronic Acid	-2.36	-0.15	18.55	7	LYS244,THR456, GLU455,LYS318,	2.389558571

Among the 8 qualified PCs, α - copaene indicatesthe highest binding affinity of -6.03 kcal/Mol with an ligand efficiency of -0.38; inhibition constant of 37.96µm and having a conventional Hydrogen bond withG,L,N @ 2, 4&8 respectively. The rest top 3 PCs are as follows: delta-Cadinene with second highest having a binding affinity of -5.78 kcal/Mol and Dauca-5, 8-diene with third highest having binding affinity of -5.66kcal/Mol against the STAT3 protein. The details for PCs No. 5-to-8 may be viewed in Table 4.

While making a comparison with the docking results of Za with osteosarcoma's STAT3 protein it is found that Za has an binding affinity of only(-)2.36 kcal/mol, which comparatively less than all the 8 qualified PCs of the Black ginger (house hold functional food). And is 2.55 times less than α-copaene - the best qualified

Tumors (uniform\poorly differentiated) in particular and even cancers (well differentiated) have high P demand, utilization and are efficient min doing so. Sarcomas are tumors. Za has P which is to the disadvantage. Again, Copane does not have O which is add on advantage as because O is not released at (drug delivery nor on to any adjunct medicament\supplement) site for there is no disassociation as Copane does

not have O atom. Furthermore, α‑copaene $C_{15}H_{24}$ Mw 204.4 and Za $C_5H_{10}N_2O_7P_2$ Mw 272 exert near equal tissue perforation force (be correlated with Figure – 7). Therefore, Copane posits well as a stand-alone compound for therapeutics cum supplement and Black ginger (whole) as a versatile functional food in the management of Sarcoma. This communication also draws upon our long involvement in Brain Malaria [26-28]; Cancer [29]; Covid-19 care [30;31]; SARS drug discovery [32;33] in-silico [34] and Medical Meteorology [35-37] studies.

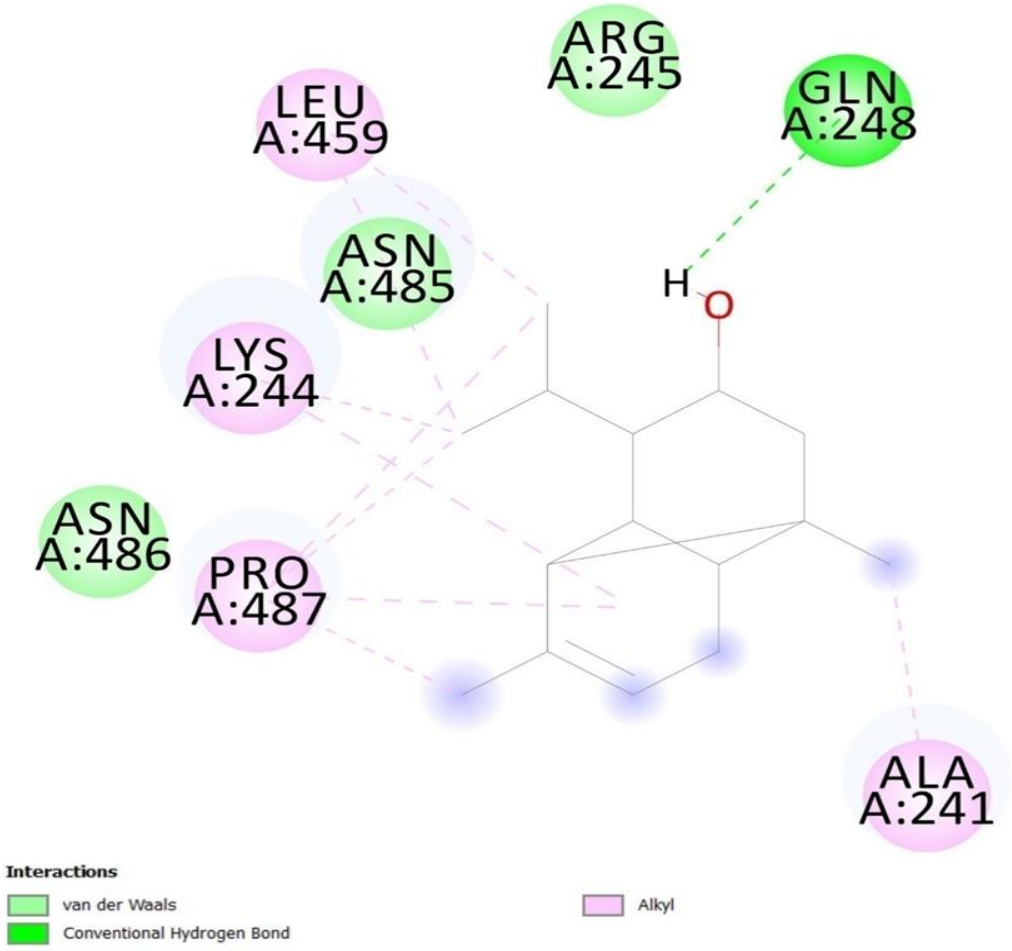

Figure 1: 2D-interaction of α‑copaene with STAT3 protein of Osteosarcoma

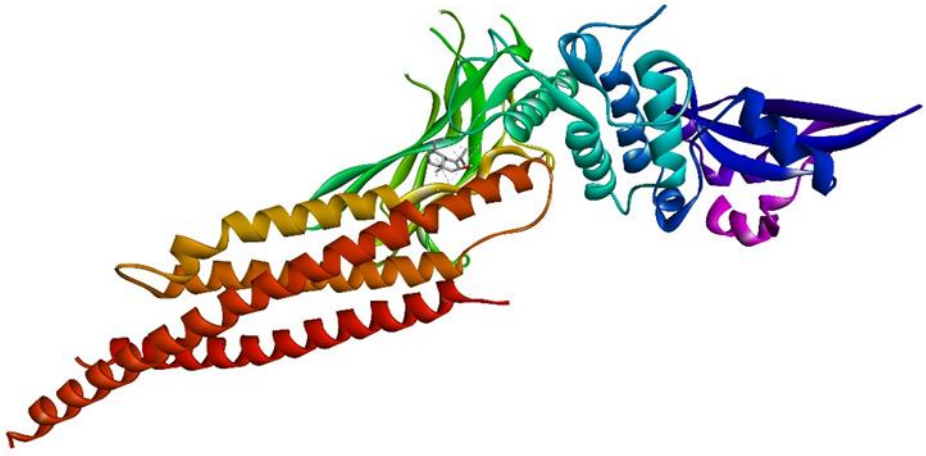

Figure 2: 3D-interaction of α‑copaene with STAT3 protein of Osteosarcoma

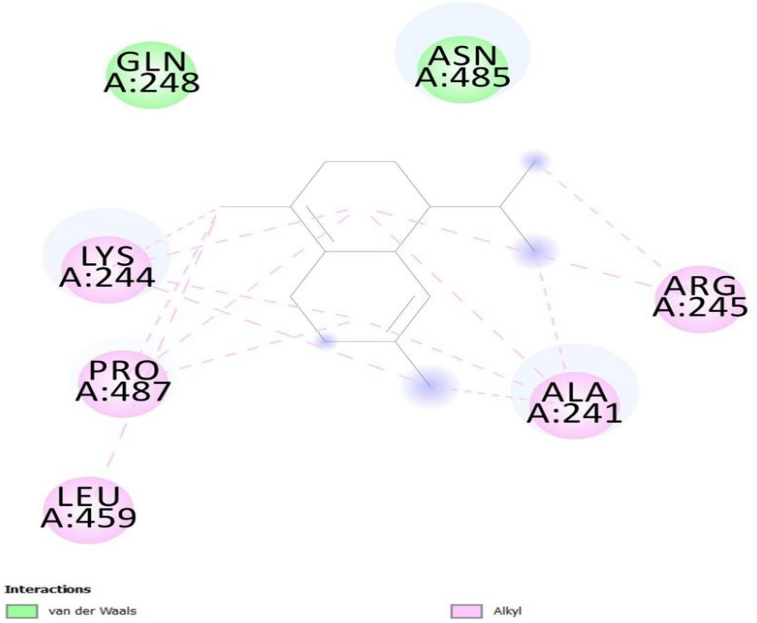

Figure 3:2D-interaction of delta-Cadinene with STAT3 protein of Osteosarcoma

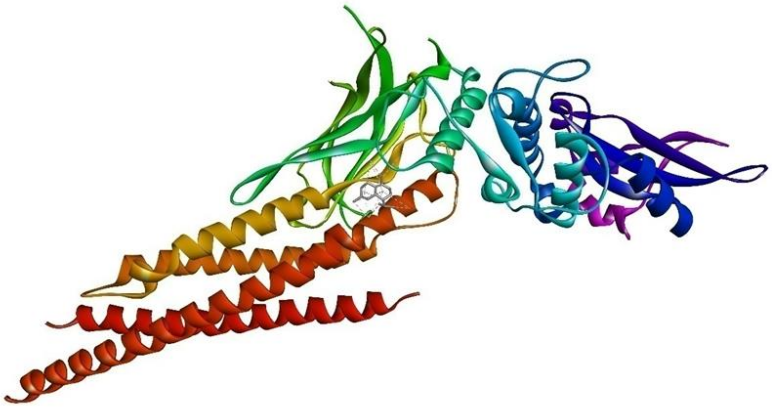

Figure 4: 3D-interaction of delta-Cadinene with STAT3 protein of Osteosarcoma

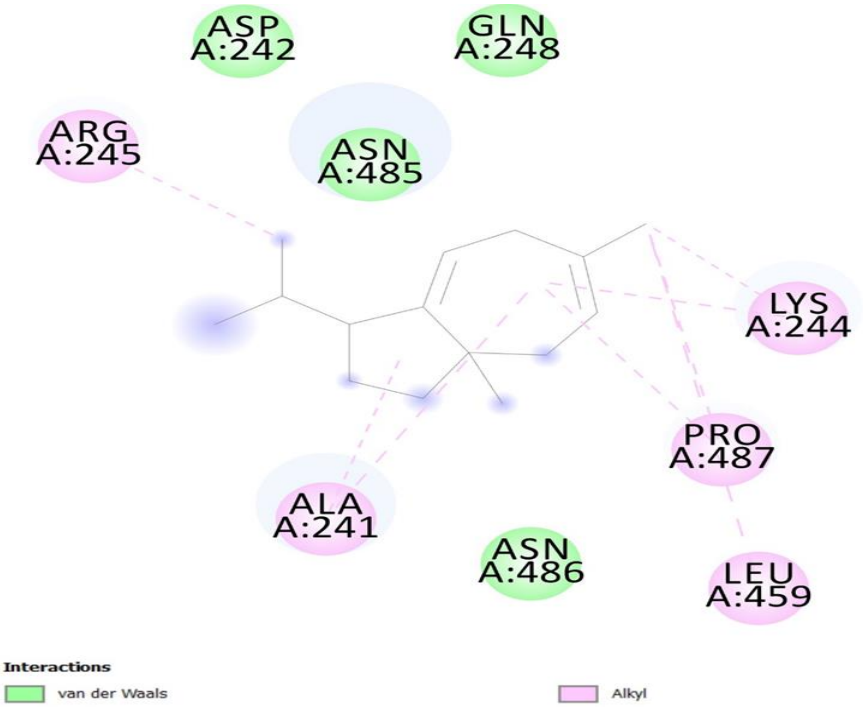

Figure 5: 2D-interaction of Dauca-5,8-diene with STAT3 protein of Osteosarcoma

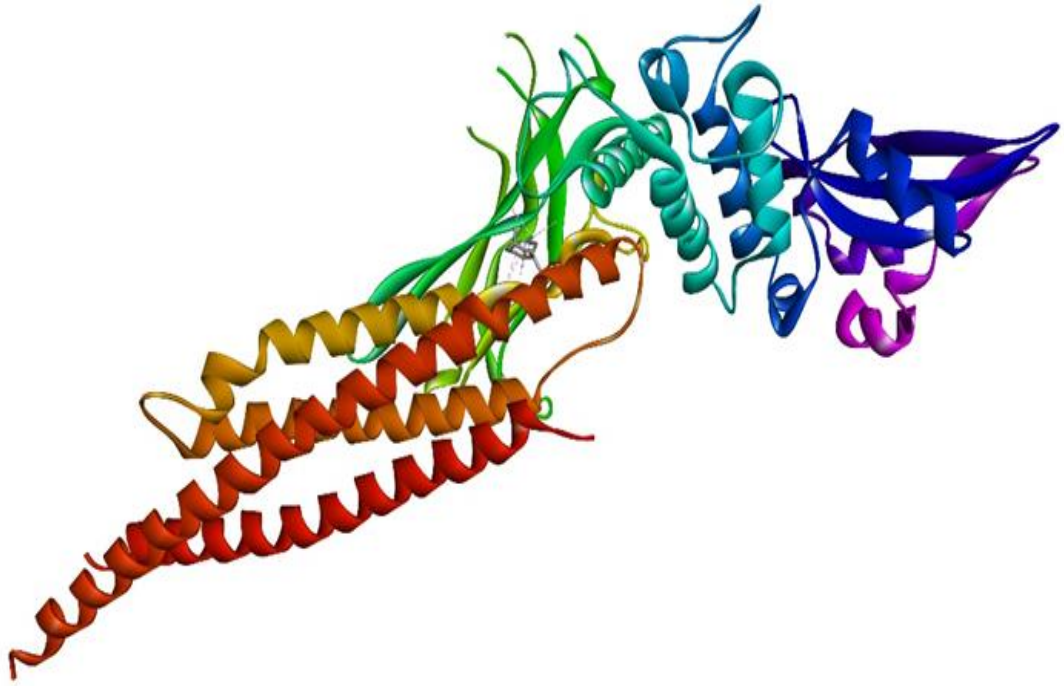

Figure 6: 3D-interaction of Dauca-5,8-diene with STAT3 protein of Osteosarcoma

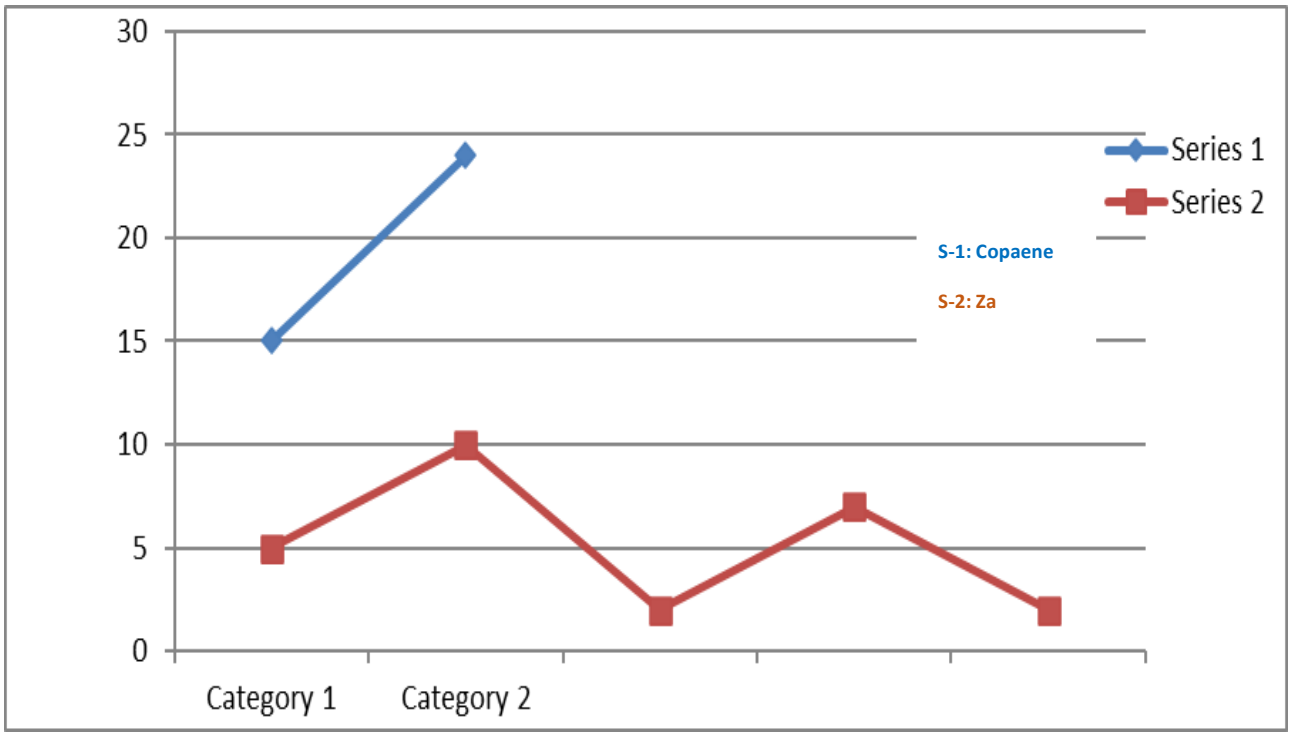

Figure 7: Graphical representation

Discussion

Kaempferia parviflora (Black ginger) is a medicinal plant. As a whole or its extracts have historically been used as health tonic in many parts of south-east Asia with reports about its medical properties; to treat various diseases including cancer [38]. It has 42 PCs. In this communication all the 42 PCs were tested in-silico against the STAT3 protein of Osteosarcoma. Only 8 of the 42 PCs qualified the Toxicity tests which also successfully passed all the mathematical parameters of the Lipinsk's rule of 5. And, PC α-copaene indicated the highest binding affinity against the STAT3

protein of human osteosarcoma (from amongst the 8). For comparison in-current use allopathic anti-sarcoma drug 'zoledronic acid' was used as the compare & contrast candidate. Interestingly, zoledronic acid indicates lower binding affinity (likeness) than all the 8 PCs of *Kaempferia parviflora*. Moreover, α-copaene is composed only of H &C atoms which makes it additionally attractive as a possible safe & long in-blood-life intravenous application candidate – pharmacologically. Furthermore (as an advantage of high order) all the 8 PCs can be separately encased (to attain high efficiency) in one single pill using Nano Technology [39].

Functional Food as Support

Zoledronic Acid i.e., bisphosphonate is administered @ 4-5mg/ml total 5ml at an interval of 21-30 days (net potency being 0.8-1 mg\ml per sitting as IV + admixed into physiological saline; case specific variation).

α - copaene - has anti-cancer activity**; is** a hydrocarbon sesquiterpene (oily liquid \resin viscous or on drying). **delta-Cadinene -** inhibits growth of ovarian cancer via caspase-dependent apoptosis and cell cycle arrest (anti-neoplasam); anti filarial; anti-bacterial; anti-vectors- **{Culicidae** }i.e., effective for poikilo & homeotherms. **Dauca - 5,8 - diene –** is used in diagnosing, treating, and monitoring the treatment of low neutrophil – Liquid cancers (fusariosis) and scedosporiosis (Mycosis). **α - cadinol -** act as anti-fungal; as hepato-protective, and as possible anti-drug-resistant in tuberculosis (sesquiterpenoid). **5,7 - dimethoxyflavone -** Helps in lipid energy production; metabolism; anti-inflammatory; apoptosis. **Epi - α - muurolol -** anti-micrbiol; fungicide; also produced by marine creatures & bacteriums; is a sesquiterpene. **α - pinene -** Versatile: antibiotic resistance modulation, anticoagulant, antitumor, antimicrobial, antimalarial, antioxidant, anti-inflammatory, anti-*Leishmania*, and analgesic effects. **Borneol –** non oxidized precursor of Camphor (camphor is used in skin pathologies including FDA-approved treatments as a common ingredient in remedies applied to the skin for cough and skin irritation\pruritus**).**

Figure - 8

Zingiber officinale:::::::::::::::::::::::::::: Kaempferia parviflora

Comparative images of the 2 ginger types for topical levity; Downloaded with Thanks from www.Zingiberon drying moiety yields remain constant. Kaempferia on drying loses numerous constituents (degeneration). Contrasting effect on physiology reflected in comprehensive pathological tests in healthy (supporting info).
NOTE: Kaempferia parviflora has violet tinge while *Curcuma Caesia* (Black Curcumin\Kali Haladi) induces sleep & is also effective in Sarcoma) is blue; either rhizome are bi-layered [40].

Table – 7 indicates possible ways to harness the benefits of *Kaempferia parviflora* in adult Sarcomas. Fixed doses have numerous advantages specially introduction; withdrawal; clinical assessment; natural resource utilisation; sustainable employment; carbon foot print. Nano technology can be utilised i.e., alike marriage of orient & occident [41].

<table>
<tr><td>#</td><td>a</td><td>b</td><td>c</td><td>d</td><td>e</td><td>f</td><td>g</td><td>h</td><td>i</td><td>j</td><td>k</td></tr>
<tr><td>SL</td><td>Za</td><td>Copaene</td><td>Cadinene</td><td>Dauca - diene</td><td>Cadinol</td><td>dimethoxyflavone</td><td>muurolol</td><td>Pinene</td><td>Burneol</td><td>Admix</td><td>Kp</td></tr>
<tr><td>1</td><td rowspan="2">1-to-1.5mg IV @ sub-clinical potency + b-to-i severally as oral adjunct/supl. as indicated in respective column</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>2</td><td rowspan="6">1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>3</td><td></td><td rowspan="5">1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>4</td><td></td><td>1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>5</td><td></td><td>1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>6</td><td></td><td>1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>7</td><td></td><td></td><td></td><td></td><td rowspan="4">1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td rowspan="4">1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td></tr>
<tr><td>8</td><td></td><td></td><td></td><td></td><td>1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>40-60mg</td><td></td><td></td><td></td><td></td></tr>
<tr><td>9</td><td></td><td></td><td></td><td></td><td></td><td></td><td>1 mini-tablet OD for 15 continuous days post IV. Post prandial + H2O ad-libitum.</td><td>300-500mg admix of b-to-i</td><td></td></tr>
<tr><td>10</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>1 standard tablet. Post Za IV ; 5 doses i.e., 1 pill every 3rd day; (nano tech based)</td><td>500 – to - 1000mg</td></tr>
<tr><td>11</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Whole bark; dried. Capsule form @ 1 cap daily\alternate day inter Za IV period. [No b-to-i]. FUNCTIONAL FOOD</td></tr>
<tr><td>12</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="12">Za represents all that & those pharma moieties (including repurposed ones) that are currently used clinically, worldwide. We have no indulgence. Za is taken herein as it is considered as a Champion among the gamut; only as a candidate case for topical levity. The PCs are available in the market as synthetic & as natural extracts. Hospital based formulating chemists & dispensing clinicians can hand-make & administer under superintendence. In place of PC whole herb can be used as Functional Food during inter-injection period with lovely results (supported with fluids; sweetened food & oral rehydrates).</td></tr>
</table>

Conclusion

This in silico investigation predicts that 8 natural CPs of the *Kaempferia parviflora* (Black ginger) can be expected as drug candidates in near future in human\veterinary pathologies that are associated with the expression of STAT3 protein

viz., osteosarcoma. It posits as good candidate for scholarly focus & commercial investments formore in-depth study (in –field; in vivo and in vitro) and specially for Osteosarcoma for which there is a crying need in the medico clinical market.

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Declarations of interest

Authors declare that they have no conflict of interest. This study is non-commercial; not funded; non donor driven.

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