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Physicochemical and pharmacokinetic Studies of Potential Drug Target Against Anti Diabetic Agent *Zingiber officinale*.

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Abstract:

Diabetes mellitus is a global health issue that requires research into new treatment approaches. An anti-diabetic agent is any drug or substance that acts on glucose metabolism, enhances insulin sensitivity, or controls blood sugar levels in order to assist treat or manage diabetes mellitus. These agents may be herbal remedies, prescription medications, or lifestyle changes meant to manage the signs and consequences of diabetes. The herb ginger, Zingiber officinale, has long been known for its therapeutic benefits, which include the possibility of anti-diabetic effects due to the bioactive chemicals in the root. In this study, we investigated the interaction between natural chemicals from Z. officinale and important molecular targets implicated in the etiology of diabetes using in-silico analysis and molecular docking experiments. We identified significant protein targets, such as alpha- amylase, alpha-glucoside, and insulin receptor, and used computational algorithms to pick notable compounds from ginger, such as gingerols, shogaols, and paradols. The Z. officinale compounds may have anti-diabetic effects by modulating important enzymes involved in insulin signaling pathways and glucose metabolism. These molecular mechanisms may be the basis for these benefits. These results offer insightful information for additional experimental validation and the creation of innovative therapeutic medicines for the treatment of diabetes.

Keyword: Diabetes Mellitus, Zingiber officinale, ADMET, Anti-Diabetic.

INTRODUCTION

Elevated blood glucose levels are the hallmark of diabetes, a chronic medical illness. It is mainly caused by problems with either the action or synthesis of insulin. The hormone insulin, which is secreted by the pancreas, is essential for controlling blood sugar levels(1). Blurred vision, weariness, increased thirst, and frequent urination are among symptoms. Type 1 Diabetes: Is an autoimmune disease in which the body is unable to manufacture glucose, a hormone that aids in blood sugar regulation. Type 2 Diabetes: A more prevalent condition when the body either grows sensitive to insulin or produces insufficient amounts of it, frequently due to lifestyle reasons(2).

Zingiber officinale, commonly known as ginger, is a flowering plant whose rhizome (underground stem) is widely used as a spice and for its medicinal properties(3). Reactivity of oxygen species (ROS), one type of free radical that is overproduced, have been linked to the onset of numerous chronic illnesses(4). Many natural goods, including fruits, vegetables, cereals, edible flowers, medicinal herbs, and herbal infusions, have been shown to have antioxidant potential. Here's an overview(5)

Biological Properties:

1. Family- Zingiberaceae, 2. Common Name- Ginger, Ginger Root, 3. Parts Used- Rhizome

Chemical contituents of zingiber officinale:

Uses: For millennia, ginger has been utilized in conventional medicine. Here are a few possible health advantages of it. It can be consumed in the form of juice or oil, dried, powdered, or fresh. The medicinal properties are digestive aid, anti inflammatory, blood sugar regulation, menstrual pain relief(6).

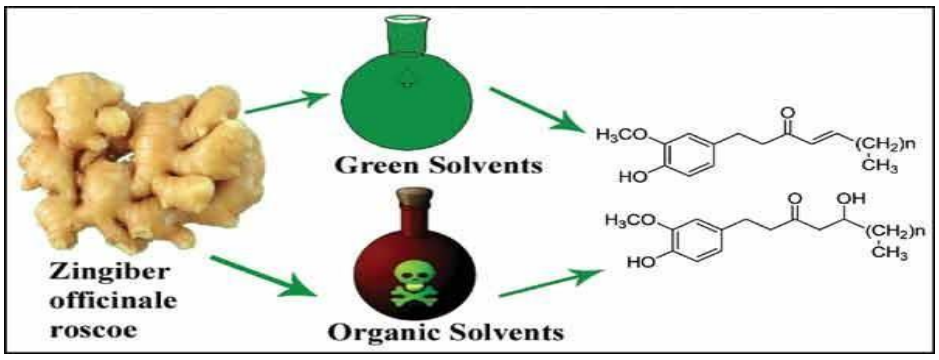


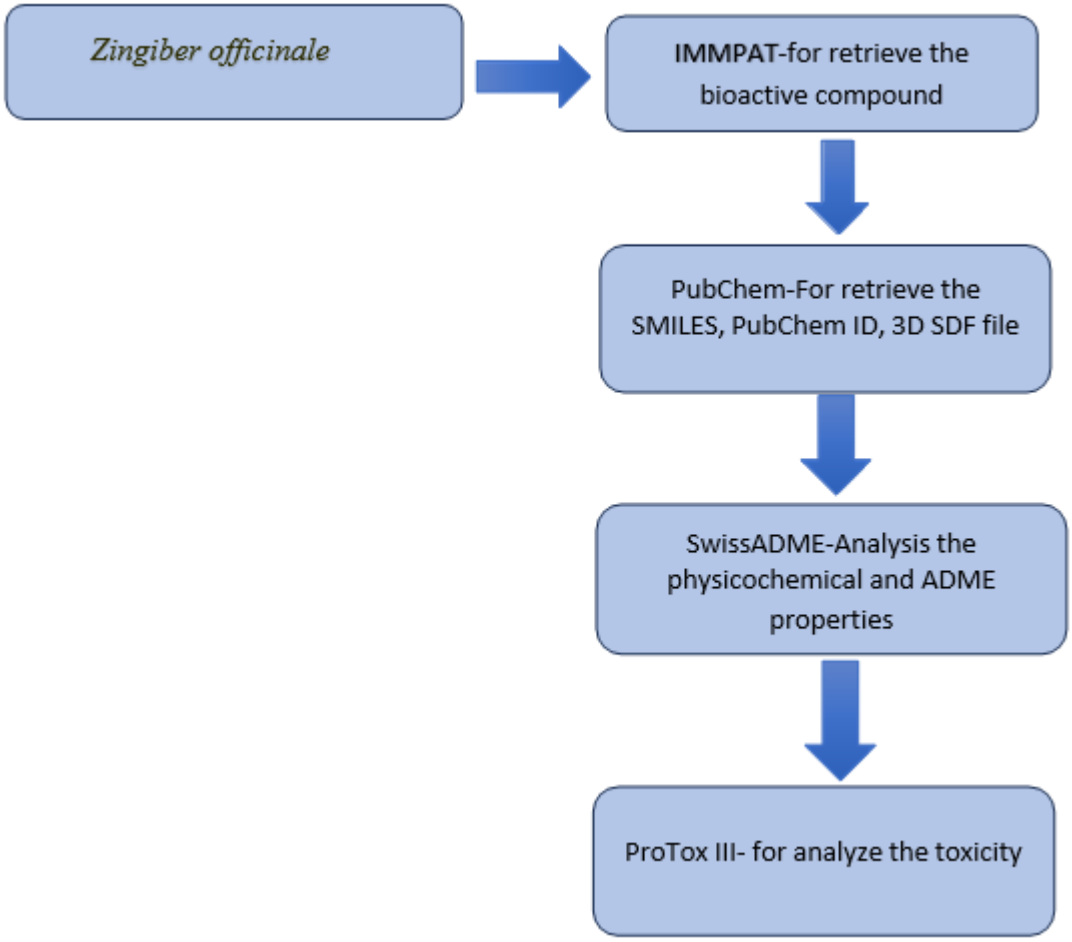
Fig.1. Pant and chemical composition of ginger

The terms Absorption, Distribution, Metabolism, Excretion, and Toxicity are combined to form ADMET(7). It provides a crucial framework for pharmacology and drug development, helping scientists assess a drug's possible safety profile and how it acts in the body(8). Overall, ADMET is crucial for

forecasting how a medication will work in people, helping to enhance drug design and limit dangers in clinical use(9).

2. METHODOLOGY

2.1. A flow chart of physiochemical properties and pharmacokinetic activity:



2.2. To determine the bioactive compound by using the IMMPAT webtools:

The immpat wed tools was used for the determination of bioactive compound and its IMPPAT (2.0) is a hand curated database that includes 1742 Indian plants for medicinal purposes, 9596 phytochemicals, which and 1124 therapeutic uses. It spans 27074 plant- phytochemical connections and 11514 plant-therapeutic linkages. This is the first step towards achieving our goals. And more data are collected from

the Pubchem webtools. In Pubchem webtools we retrieved the SMILES, molecular formula and pubchem ID also. The retrieved data are mention in table.1.

Table .1- To retrieved the data by using the IMMPAT webtools.

S. No.	Bioactive compounds	Pubchem ID	Molecular formula	SMILE
1	3-Methylbutanal	11552	C5H10O	CC(C)CC=O
2	Zingerone	31to211	C11H14O3	CC(=O)CCC1=CC(=C(C=C1)O)OC
3	Zingiberene	92776	C15H24	CC1=CC[C@@H](C=C1)[C@@H](C)CCC=C(C)C
4	Citral	638011	C10H16O	CC(=CCC/C(=C/C=O)/C)C
5	Benzaldehyde	240	C7H6O	C1=CC=C(C=C1)C=O
6	Eucalyptol	2758	C10H18O	CC1(C2CCC(O1)(CC2)C)C
7	Camphor	2537	C10H16O	CC1(C2CCC1(C(=O)C2)C)C
8	Menthone	26447	C10H18O	C[C@@H]1CC[C@H](C(=O)C1)C(C)C
9	Menthol	1254	C10H20O	CC1CCC(C(C1)O)C(C)C
10	Octanal	454	C8H16O	CCCCCCCC=O
11	alpha-Santalol	5281531	C15H24O	C/C(=C/CCC1(C2CC3C1(C3C2)C)C)/CO
12	2-Heptanone	8051	C7H14O	CCCCCC(=O)C

2.3. 2D Molecular structure: The 2D molecular structure are draw by using the Chem sketch webtools with the help of SMILES. The all 2D structure is draw in below:

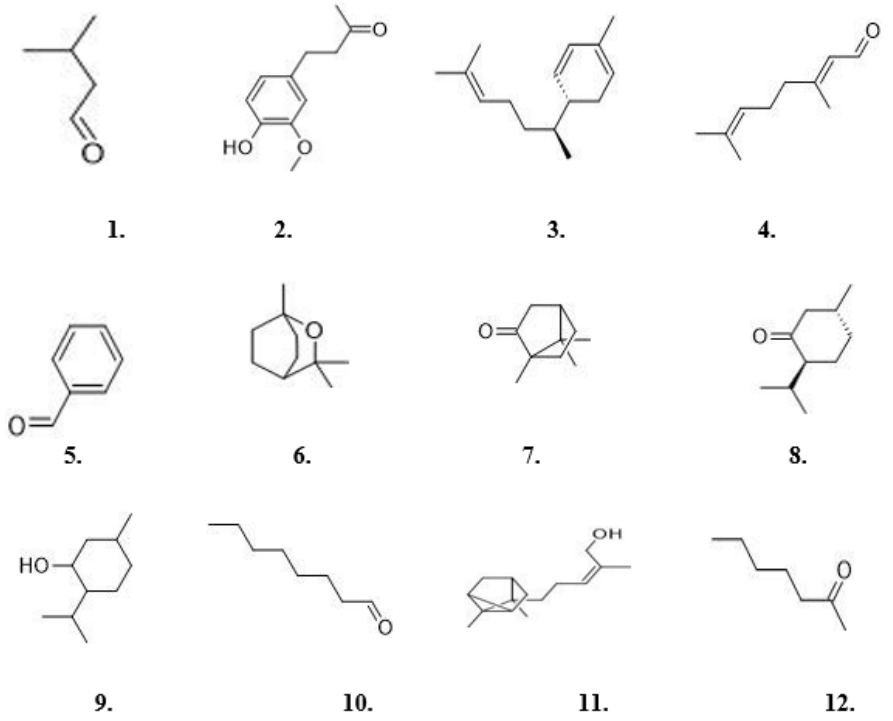


Fig. 2. The 2D structure of zingiber officinale: 1) 3-Methylbutanal, [2] Zingerone, [3] Zingiberene, [4] Citral, [5] Benzaldehyde, [6] Eucalyptol, [7] Camphor, [8] Menthone, [9] Menthol, [10] Octanal, [11] alpha-Santalol, [12] 2-Heptanone.

3. RESULT AND DISCUSSION

3.1. To analysis the physical and chemical properties of bioactive compound:

Table-2. To analysis the physicochemical properties:

S. NO.	Phytochemical compound	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	TPSA	%Abs.	Log Po/w (iLOGP)
1	3-Methylbutanal	86.13 g/mol	2	1	0	17.07 Å²	103.11	1.49
2	Zingerone	194.23 g/mol	4	3	1	46.53 Å²	92.94	2.09
3	Zingiberene	204.35 g/mol	4	0	0	0.00 Å²	109	3.63

4	Citral	152.23 g/mol	4	1	0	17.07 Å²	103.11	2.51
5	Benzaldehyde	106.12 g/mol	1	1	0	17.07 Å²	103.11	1.36
6	Eucalyptol	154.25 g/mol	0	1	0	9.23 Å²	105.81	2.58
7	Camphor	152.23 g/mol	0	1	0	17.07 Å²	103.11	2.12
8	Menthone	154.25 g/mol	1	1	0	17.07 Å²	103.11	2.4
9	Menthol	156.27 g/mol	1	1		20.23 Å²	102.02	2.55
10	Octanal	128.21 g/mol	6	1	0	17.07 Å²	103.11	2.29
11	alpha-Santalol	220.35 g/mol	4	1	1	20.23 Å²	102.02	2.93
12	2-Heptanone	114.19 g/mol	4	1	0	17.07 Å²	103.11	2.09

- When we analysis the physicochemical properties by using the SwissADME webtools then they find the some datas like molecular weight, no. of hydrogen donor, no. of hydrogen acceptor , TPSA, and log Po/w.
- After that we analysis all the data and find the best percentage of abs. is Zingiberene(3), Eucalyptol(6) and ehw the %of abs. is high the the TPSA value is low , the Standard TPSA value is 140 A2 AND above the % of abs. very poor and the TPSA value is 90 A2 and less the the % of abs. is best. In this all compound are follow RO5 rules.
- For optimal oral and intestinal absorption, an oral medication ought to have a LogP value <5, preferably between 1.35 and 1.8, in accordance with Lipinski's Rule of 5. According to this the best hydrophilic compound is Benzaldehyde(1.36), 3-Methylbutanal(1.49) and more lipophilic properties is Zingiberene(3.63) and alpha-Santalol(2.93) , all data are meantion in below table -2.

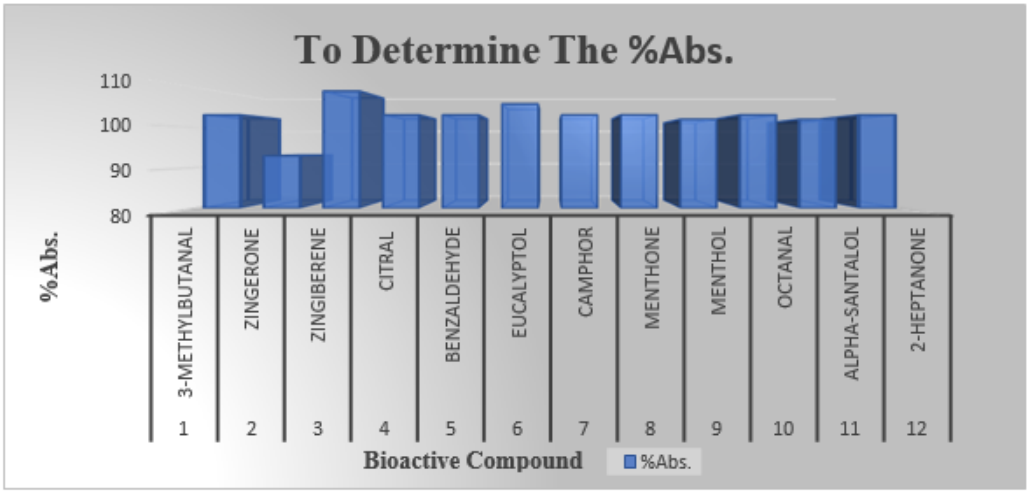


Fig. 3- To represent the % of abs. by using graph

3.2. To the analysis of pharmacokinetic properties:

Table-3. To the predication of pharmacokinetic properties:

S. No.	Bioactive Compounds	GI Absorption	BBB Permeant	P-Gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log Kp(Skin Permeation)
1	3-Methylbutanal	High	Yes	No	No	No	No	No	No	-6.12 Cm/S
2	Zingerone	High	Yes	No	Yes	No	No	No	No	-6.70 Cm/S
3	Zingiberene	Low	No	No	No	Yes	Yes	No	No	-3.88 Cm/S
4	Citral	High	Yes	No	No	No	No	No	No	-5.08 Cm/S
5	Benzaldehyde	High	Yes	No	Yes	No	No	No	No	-5.90 Cm/S
6	Eucalyptol	High	Yes	No	No	No	No	No	No	-5.30 Cm/S
7	Camphor	High	Yes	No	No	No	No	No	No	-5.67 Cm/S
8	Menthone	High	Yes	No	No	No	No	No	No	-5.08 Cm/S
9	Menthol	High	Yes	No	No	No	No	No	No	-4.84 Cm/S

10	Octanal	High	Yes	No	No	No	No	No	No	-5.15 Cm/S
11	Alpha-Santalol	High	Yes	No	No	Yes	Yes	No	No	-4.83 Cm/S
12	2-Heptanone	High	Yes	No	No	No	No	No	No	-5.59 Cm/S

- In this evalution we find the pharmacokinetic properties like- GI Absorption, BBB Permeant, P-Gp Substrate, CYP1A2 Inhibitor , CYP2C19 Inhibitor, CYP2C9 Inhibitor, CYP2D6 Inhibitor, CYP3A4 Inhibitor and Log Kp(Skin Permeation) by using the swiss ADME webtools with the help of SMILES.
- We find different parameter and different best bioactive compounds. In the GI absorptionwe analysis that only one compound is show the poor absorption is Zingiberene(3) and restall the compound show the high GI absorption. Mentain in table-3.
- In the distribution, we retrieved the bioactive compound by using the swissADME . Thanthey found the only one compound Zingiberene(3) should not be cross the BBB Permeantand rest of all the compound are cross the BBB Permeant for the drug distribution. Mentionin table-3.
- At last we evalute the metabolism and excretion we found the some of compound they donot show any Inhibitor like 3-Methylbutanal(3), Citral(4), Eucalyptol(6), Camphor(7), Menthone(8), Menthol(9), Octanal(10), 2-Heptanone(12).
- In CYP1A2 Inhibitor we found only two inhibitor first is Zingerone(2) and second is Benzaldehyde and rest of all the compound are not show any inhibitor. And the next we determine the CYP2C19 Inhibitor and CYP2C9 Inhibitor both are inhibit the same compounds is Zingiberene(3) and Alpha-Santalol(11) and remaning of all compound are not show any inhibition. Mention in table-3.
- In the final we determine the Log Kp(Skin Permeation) also by using the swissADME. Inthis properties the normal range from -6.10 to -0.76 cm/s. In this retrieval we found the highest skin permeation is Zingiberene(-3.88 cm/s) and the lowest skin permeation is Zingerone(-6.70 cm/s) mention in table -3

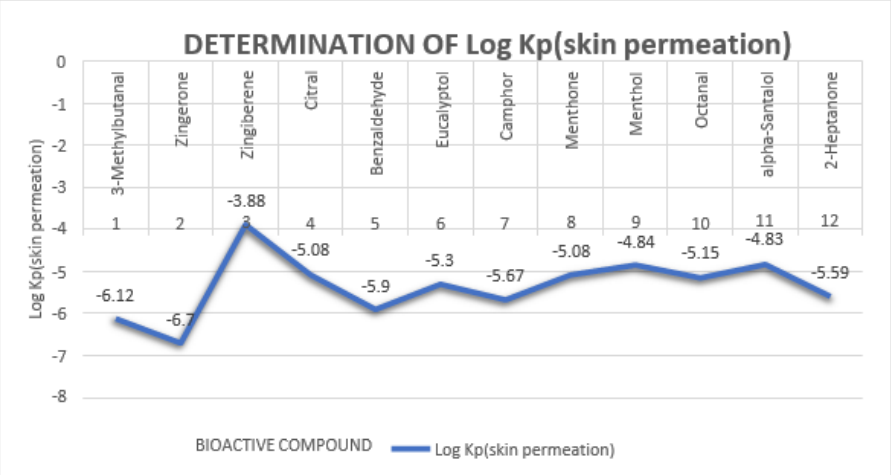


Fig. 4- To represent the Log Kp(skin permeation) by using graph

S.No.	Bioactive compo	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	LD50(mg/kg)	Toxicity Class
1	3-Methylbut	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	2490mg/kg	5
2	Zingerone	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	2580mg/kg	5
3	Zingiberene	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	1680mg/kg	4
4	Citral	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	500mg/kg	4
5	Benzaldeh yde	inactive	active	inactive	inactive	active	active	active	inactive	inactive	28mg/kg	2
6	Eucalyptol	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	inactive	2480mg/kg	5
7	Camphor	inactive	active	inactive	inactive	inactive	inactive	inactive	inactive	inactive	775mg/kg	4
8	Menthone	inactive	active	inactive	active	inactive	inactive	active	inactive	inactive	1190mg/kg	
9	Menthol	inactive	inactive	inactive	active	inactive	inactive	active	inactive	inactive	940mg/kg	4
10	Octanal	inactive	active	inactive	inactive	inactive	inactive	inactive	inactive	inactive	5000mg/kg	5
11	alpha-Santalol	inactive	inactive	inactive	active	inactive	inactive	inactive	inactive	inactive	3800mg/kg	5
12	2-Heptanone	inactive	active	inactive	inactive	inactive	inactive	inactive	inactive	inactive	5000mg/kg	5

- The ProTox 3.0 webtools are used for the determination of toxicity end point, toxicity class and LD 50 value by the help of SMILES.

- They have various types of toxicity end point like Hepatotoxicity, Neurotoxicity, Nephrotoxicity, Respiratory toxicity, Cardiotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity and Cytotoxicity.

- Firstly we retrieved all the compound than they found some compound like 3-Methylbutanal(1), Zingerone(2), Zingiberene(3), Citral(4), and Eucalyptol(6) are inactive for all the toxicity end point.

- In Neurotoxicity, there are two compound Benzaldehyde(5) and Menthone (8) are highly toxic and two more compound are toxic like Camphor(7) and Octanal(10) and remaining compound are showed non toxic in nature.

- In Respiratory toxicity, there are three compound are highly toxic Menthone(8), Menthol(9), alpha-Santalol(11), and remaning are non toxic in nature.

- In Cardiotoxicity and Carcinogenicity only one compound is highly Benzaldehyde(5) and remaning all the compound are show non toxic in nature.

- At last we retrieved the last toxicity endpoint is Immunotoxicity, two compound show the highly toxic Menthone(8) and Menthol(9) and remaning all the compound are non toxic mention in table -4.

- The more toxic of all bioative is Benzaldehyde(5). It is highly toxic in nature. And also we retrieved the LD 50 dose than they found the best LD 50 values is 2-Heptanone(12), Octanal(10) mentain in table -4

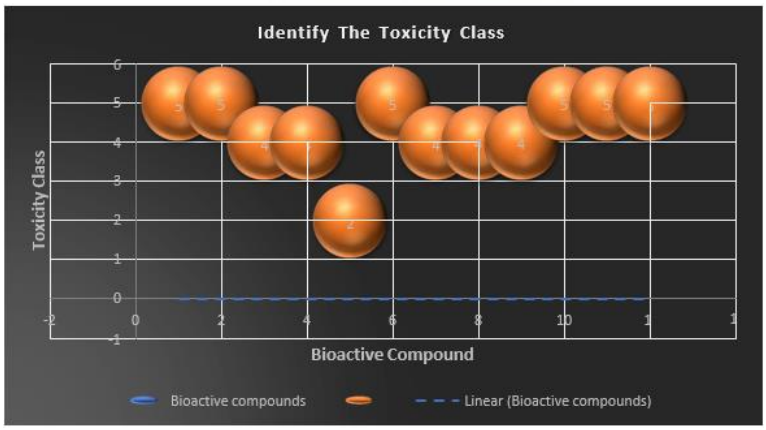


Fig.5- to represent the toxicity class by using graph

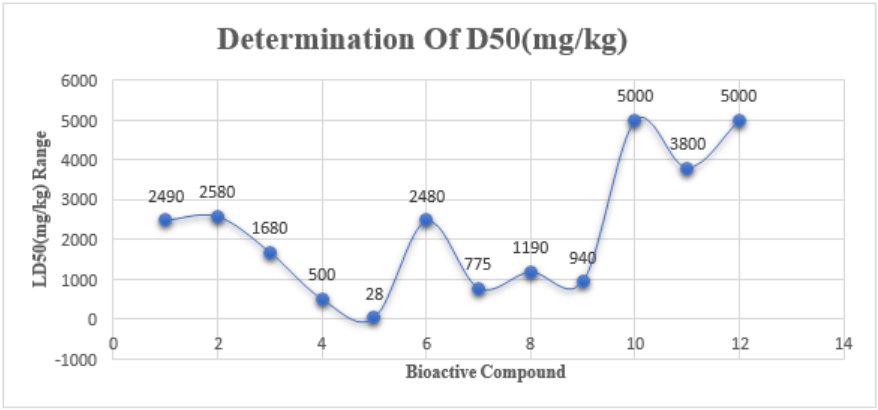


Fig.-5. To represent the LD50 value by using graph

4. CONCLUSION

- In the final when we retrieved all the data like physicochemical, pharmacokinetic and toxicity than they found the some best compound out of twelve. The all bioactive compound are followed RO5 rules. And the high GI absorption of all compound except Zingiberene. Zingiberene is a low GI absorption.
- In pharmacokinetic study we find the best Log kp value is Zingiberene(-3.88 cm/s) and the toxicity class is 3-Methylbutanal, Zingerone, Camphor, Menthone are 5,5,4 and 4 respectively.
- Overall research that indicated the best potential for the Anti Diabetic are 3-Methylbutanal, Zingiberene and Benzaldehyde. In future we perfome the molecular docking of these compounds.

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Conflict of Interest

All the author declare that there is no conflict of inerest.

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