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LEAD FINDING FROM WHOLE PLANT OF *CURCUMA LONGA* WITH OXIDATIVE POTENTIAL

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ABSTRACT: The present study deals with the antioxidant activity, drug likeness score and bioactivity score of the compounds isolated from *Curcuma longa* and search lead antioxidant compound through molinspiration software. We have taken ten compounds from this plant. All the compounds were further subjected to molecular properties prediction and drug likeness by Molinspirstion and found in compliance with Lipinski's rule of five. The compounds IV, V, IX, X fulfill Lipinski's rule and show good drug likeness score. Milog P of these compounds was found below 5 that means these shows good permeability across cell membrane. TPSA below 160 $Å^2$, *n* violatios =1 or <0 it means compound easily bind to receptor, molecular mass <500, *n* rotb < 5 [10], Number of hydrogen bond donors ≤ 5 (The sum of OHs and NHs), Number of hydrogen bond acceptor ≤ 10 (The sum of Os and Ns). Compounds I-X were taken further calculation of bioactivity score by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. Our study shows that compound IV α-bisabolol has good drug likeness score with no violations and good bioactivity score as compared to BHT (standard compound). So, compound IV α-bisabolol can be a lead compound with antioxidant activity from *Curcuma longa*.

INTRODUCTION: Antioxidants are naturally occurring molecules capable of counteracting the damaging effects of oxidation in the body. They are a diverse class of compounds that include nutrients (vitamins, minerals) as well as enzymes (proteins in the body that catalyze reactions) and amino acids, and are believed to play a vital role in preventing the development of many diseases.

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Free radicals are highly reactive molecules with an odd number of electrons generated from oxygen; they can damage various cellular structures, such as DNA, proteins, and cellular membranes. It is one of the principal theories to explain the cause of aging in the body. In the skin, free radical damage leads to the breakdown of collagen fibers, resulting in skin relaxation and wrinkled appearance. They also may lead to inflammation, which is thought to play an additional role in skin aging. Oxygen is most prevalent element in the earth's crust. It exists in air as a diatomic molecule. Reactive oxygen species are involved in several disorders. The harmful action of the free radicals can, however, is blocked by antioxidant substances which scavenge the free radicals and detoxify the organism.

Oxidative stress is considered to play a pivotal role in the pathogenesis of antiaging & several degenerative diseases, such as atherosclerosis, cardiovascular disease, cancer [1, 2]. Therefore, plant derived antioxidants are now receiving a special attention. A large number of phenolic compounds present in vegetable, foods, such as fruits and nuts, peanuts, essential oils, aromatic plants have been reported to possess good antioxidant properties [3-4].

Curcuma longa (Turmeric) exhibits antioxidant activity and protect from free radical damage. Curcumas also exhibits anti-tumor activities and prevent cancer. It inhibits the topoisomerase enzyme, which is required for cancer. Turmeric held a place of honor in Indian traditional Ayurvedic medicine.

In Ayurvedic, it was prescribed for the treatment of many medical problems ranging from constipation to skin diseases. It was used as digestive aid and treatment for fever, inflammation, wounds, infections, dysentery, arthritis, injuries, trauma, jaundice and other liver problems.[5]

On the basis of literature survey we find many compounds isolated from *Curcuma longa* as β-bisabolene, linoleic acid, α-selinene, α-bisaboloonel, β-pinene, Curcumin-I, Curcumin II, Curcumin III, Limonene, Carvone etc. In present study we evaluate compounds for antioxidant activity. The objective of our research work was to compare different compounds which are isolated from *Curcuma longa* with standard compound BHT (butylated hydroxy toluene) on the basis of Lipinski,s Rule and physiological interpretation by Molinspiration software.

MATERIALS AND METHODS:

Lipinski's Rule: Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME). The rule is important for drug development where a pharmacologically active lead structure is optimized stepwise for increased activity and selectivity, as well as drug like properties. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bond and a higher lipophilicity. Physicochemical parameters play a vital role in generation and escalation of bioactivity of chemical entity [6].

Molinspiration, web based software [6, 7] was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors and used to predict the permeability of molecule across the cell membrane. The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment based contributions in which O- and N- centered polar fragments are to be considered and calculated by surface areas that are occupied by nitrogen and oxygen atoms and by hydrogen atoms attached to them [8]. TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, $CaCO_2$ permeability and blood brain barrier penetration, bioavailability.

Thus, the TPSA is closely related to the hydrogen bonding potential of a compound. Method for calculation of molecular volume developed at Molinspiration is based on group contributions. Number of Rotatable Bonds – (n rotb) it measures molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [9]. Rotatable bond is defined as any single non-ring bond, bounded to non-terminal heavy atom.

Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecular size and flexibility and presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others [6].

Orally Lipinski's rule states:

- An octanol-water partition coefficient log P not greater than 5
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- A molecular mass less than 500 daltons
- No more than one number of violations.

Bioactivity Score [6, 7, 10]: Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend , kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www. molinspiration.com). Calculated drug likeness score of each compounds and compared with the specific activity of each compound, and the results were compared with standard drug.

For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive.

RESULT

Physiochemical properties: The physicochemical properties as molecular formula, solubility of the compounds (I-X) are summarized in **Table 1**.

TABLE 1: PHYSICO-CHEMICAL PROPERTIES OF THE COMPOUNDS

Compound Code	Compound Name	Molecular formula	Solubility	IUPAC Name
I	β-bisabolene	$C_{15}H_{24}$	Alcohol	(S)-1-Methyl-4-(5-methyl-1-methylene-4hexenyl) cyclohexene.
II	Linoleic acid	$C_{18}H_{32}O_2$	Water	Cis,cis-9,12-octadecadienoic acid
III	α -selinene	$C_{15}H_{24}$	Alcohol	1, 2, 3, 4, 4a, 5, 6, 8a-octahydro-4a, 8-dimethyl-2-(prop-1-en-2-yl)-nephthalene.
IV	α -bisabolol	$C_{15}H_{26}O$	Alcohol	6-methyl-2-(4-methylcyclohex-3-en-a-yl)hept-5-en-2ol
V	β -pinene	$C_{10}H_{16}$	Alcohol	6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane
VI	Curcumin-I	$C_{21}H_{20}O_6$	Acetone, Ethanol	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione
VII	Curcumin-II	$C_{20}H_{18}O_5$	Acetone, Ethanol	(1E,6E)-1,6-heptadiene-3,5-dione,1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)
VIII	Curcumin -III	$C_{19}H_{16}O_4$	Acetone, Ethanol	(1E,6E)-1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione
IX	Limonene	$C_{10}H_{16}$	Acetone	1-Methyl-4-(1-methyl ethnyl)-cyclohexene
X	Carvone	$C_{10}H_{14}O$	Methanol	2-methyl-5-(1-methyl ethenyl)-2-cyclohexanone
XI	BHT (butylated hydroxyl toluene) (Standard)	$C_{15}H_{24}O$	Ethanol	2,6-bis(1,1-dimethyl ethyl)-4-methyl phenol

Drug likeness calculation on the basis of Lipinski's rule of five: The drug likeness score was calculated by considering Milog P (partition coefficient), number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds, molecular weight, volume. The drug likeness score and the calculated value of various parameters of the isolated compounds (I-X) are in **Table 2**.

TABLE 2: DRUG LIKENESS SCORE FOR COMPOUNDS

S. No.	Compd. No.	miLogP	TPSA	N Atoms	n ON	N OHNH	*n* violation	n rotb.	volume	MW
1	I	5.46	0.0	15	0	0	1	4	234.878	204.357
2	II	7.583	37	20	2	1	1	15	318.839	282.46
3	III	5.239	0	15	0	0	1	1	229.95	204.357
4	IV	4,679	20.228	16	1	1	0	4	248.229	222.372
5	V	3.329	0.0	10	0	0	0	0	152.369	136.238
6	VI	2.303	93.066	27	6	2	0	8	306.636	338.359
7	VII	2.484	83.832	25	5	2	0	7	368.385	332.182
8	VIII	2.666	74.598	23	4	2	0	6	281.09	308.333
9	IX	3.615	0.0	10	0	0	0	1	157.296	136.238
10	X	2.513	17.071	11	1	0	0	1	159.478	150.221
11	XI (standard)	5.435	20.228	16	1	1	0	2	240.996	220.356

Bioactivity score of the Compounds: The Bioactivity scores of the isolated compounds (I-X) are compared with standard drug on the basis of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor in **Table 3**.

TABLE 3: BIOACTIVITY SCORE OF THE COMPOUNDS

S. No.	Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	I	-0.32	0.10	-0.87	0.15	-0.65	0.27
2.	II	0.17	0.07	-0.22	0.23	0.07	0.27
3.	III	-0.24	0.12	-0.98	0.34	-0.51	0.28
4.	IV	-0.20	0.17	-0.88	0.10	-0.52	0.36
5.	V	-0.53	-0.32	-1.45	-0.50	-0.79	-0.34
6.	VI	-0.06	-0.20	-0.26	0.12	-0.14	0.08
7.	VII	-0.04	-0.20	-0.26	0.12	-0.14	0.08
8.	VIII	0.00	-0.14	-0.26	0.25	-0.08	0.15
9.	IX	-0.91	-0.27	-2.01	-0.34	-1.38	-0.21
10.	X	-1.23	-0.30	-2.51	-0.54	-1.21	-0.45
11.	XI (standard)	-0.34	0.00	-0.48	-0.08	-0.57	-0.07

DISCUSSION: The compounds IV, V, IX, X fulfill Lipinski's rule and show good drug likeness score (Table 2). Milog P < 5. TPSA< 160 $Å^2$, *n* violations = 0 it means compound easily bind to receptor, molecular mass <500, n rotb < 5, No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. hydrogen bond acceptor ≤ 10 (The sum of Os and Ns). Compound I - X were taken further calculation of bioactivity score from Table 3. Compounds IV, V, IX, X showed good bioactivity score. Compound IV (α-bisabolol) showed good drug likeness score and bioactivity score, on comparison with other compounds.

CONCLUSION: Comparing drug likeness score and bioactivity score of compounds (I-X), Compound IV (α-bisabolol), in respect of standard BHT (antioxidant compound), showed good drug likeness score, and bioactivity score. It can be lead compound with antioxidant activity.

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