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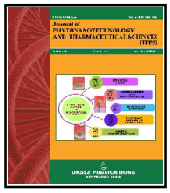

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Designing of a novel curcumin analogue to inhibit mitogen-activated protein kinase: A cheminformatics approach

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Abstract

Turmeric (*Curcuma longa* L.) is a medicinal plant used in Ayurveda, Unani and Siddha medicine as home remedies for various diseases. *C. longa*, botanically related to ginger (Zingiberaceae family), is a perennial plant with a short stem, large oblong leaves and bears ovate, pyriform or oblong rhizomes, which are often branched and brownish-yellow in colour. In recent years, extensive *in vitro* and *in vivo* studies suggested curcumin has anticancer, antiviral, antiarthritic, antiamyloid, antioxidant, and anti-inflammatory properties. Curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation, and it modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumour necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases. The derivatives of curcumin, bisdemethoxy curcumin and demethoxycurcumin also have antioxidant activity, and curcumin also reduces oxidised proteins in amyloid pathology in Alzheimer's patients. This study aims to find a novel analogue of curcumin that targets multiple pathways in the body, as curcumin is found to have low bioavailability *in vivo*. With the help of an advanced computational tool, the Analog molecules are constructed with database search and the SmiLib combinatorial library approach. Docking studies of analogues referenced to curcumin and its derivatives revealed few analogues that could be gained as drugs to inhibit MAPKs (ERK1).

1. Introduction

Turmeric (*Curcuma longa* L.) is a medicinal plant used in Ayurveda, Unani and Siddha medicine as home remedies for various diseases. *C. longa*, botanically related to ginger (Zingiberaceae family), is a perennial plant with a short stem, large oblong leaves and bears ovate, pyriform or oblong rhizomes, which are often branched and brownish-yellow in colour (Dusabumuremyi *et al.,* 2022). In recent times, traditional Indian medicine has used turmeric powder to treat biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic infections, rheumatism and sinusitis (Liu *et al.,* 2022). In China, *C. longa* is used for diseases associated with abdominal pains (Hidayat *et al*., 2022). Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from the rhizome (turmeric) herb *Curcuma longa* Curcumin has been identified as the active principle of turmeric; chemically, it is a bis-a, b-unsaturated b-diketone that exhibits keto-enol tautomerism (Karak *et al*, 2022; Tambawala *et al.,* 2022).

In recent years, extensive *in vitro* and *in vivo* studies suggested curcumin has anticancer, antiviral, antiarthritic, antiamyloid, antioxidant, and anti-inflammatory properties. An earlier study shows that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation, and it modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumour necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases (Haftcheshmeh *et al.,* 2022; Purushothaman *et al.,* 2022). COX-2 and iNOS inhibition are likely accomplished *via* curcumin's suppression of nuclear factor kappa B (NF-kB) activation. Curcumin suppresses NF-kB activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IkB) (Simu *et al.,* 2022).

The derivatives of curcumin, bisdemethoxycurcumin and demethoxycurcumin also have antioxidant activity, and curcumin also reduces oxidised proteins in amyloid pathology in Alzheimer's patients. Curcumin has various activities that help combat different diseases (Guo *et al.,* 2020; Panda *et al.,* 2022; Yuan *et al.,* 2020). Mitogen-activated protein kinase (MAPK) and NF-kappa B (NF-kappa B) signalling cascades are thought to regulate different cell survival and apoptosis mechanism (Liang *et al.,* 2018).The regulated kinase has mitogen-activated protein kinase 3 (MAPK3), also known

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as ERK1 is widely expressed with different signalling (Kciuk *et al.,* 2022; Ronkina *et al*., 2022).

As turmeric has different inflammation activity, targeting the Map kinase (MAPK1) helps to find new combinations of molecules with the help of a better computational approach to provide a novel drug molecule to cure multiple diseases.

2. Material and Methods

Based on literature studies, biologically active compounds present in Indian turmeric were retrieved from the database. Indian turmeric extracts comprise curcuminoids, the most biologically active compounds reported for various pharmacological activities and a potent inhibitor for diverse biological activities, including anti-carcinogenic, anti-inflammatory and antioxidant reported *in vitro* and *in vivo* (Howes, 2018; Vakhariya Sakina *et al*., 2016). The present protocol is the *in silico* studies to explore curcumin as a potent drug molecule for different biological targets. Curcuminoids include three active compounds: Curcumin, Demethoxycurcumin and Bisde methoxy curcumin (Sharifi-Rad *et al.,* 2020). The literature studies of curcuminoids reveal the biological activity of curcumin to be 77%, Demethoxycucumin to be 17% active and Bisdemethoxycurcumin to be 3% functional (Rajagopal *et al.,* 2020). The 3-Dimensional structure of curcumin and its derivatives was downloaded from the chEMBL (https://www.ebi.ac.uk/chembl/) database through compound search. ChEMBL or ChEMBLdb is a manually curated chemical database of bioactive molecules with drug-like properties maintained by the European Bioinformatics Institute (EBI) of the European Molecular Biology Laboratory (EMBL).

2.1 Structural analysis of curcumin and its derivatives

The two-Dimensional structures of curcumin were studied from the literature, while the three-Dimensional structures were obtained from the ChEMBL database compound search. Curcumin, a hydrophobic natural product, comprises two phenolic rings. Each ring is replaced with methoxy ether functionality in the *ortho*-position and attached by an aliphatic unsaturated heptene linker in the *para*-position with an α, α diketonic functionality on carbon-3 and -5. The electrophilic α and α-unsaturated carbonyl groups can react with a nucleophile such as glutathione 15 (Lo Cascio *et al.,* 2021). Several studies suggest that the diketone functionality can go through reversible tautomerisation between enolic and ketonicforms. Curcumin is radiant yellow at pH 2.5 to 7 and evolves to red at pH e^{-}7. Whether in solid or soluble form, curcumin goes through photodegradation upon exposure to light 17. Curcumin has a melting point of 183^{o}C, a molecular formula of $C_{21}H_{20}O_6$, and a molecular weight of 368.37 g/mol. It is not as soluble in water as in organic solvents such as dimethyl sulfoxide, ethanol, methanol and acetone (Alrawaiq *et al*., 2014; Hadi *et al.,* 2020; Kotadiya *et al*., 2015).

2.2 Retrieval and classification of targets

Protein targets for curcumin and its derivatives were predicted using a diverse range of publicly available Bioinformatics Databases and various literature studies. The ChEMBL database was used to obtain the list of protein targets based on a structure similarity search with the cutoff value of 100%. The obtained protein targets were classified under Enzymes, Non-enzymes, Transcriptional factors, Epigenetic regulators, Membrane receptors, secreted proteins, Ion channels and cytosolic proteins. Enzymes were further classified based on Enzyme Classes with the help of the UniProt (https://www.uniprot.org/) database. KEGG (https://www.genome.jp/kegg/) pathways database was used to study the targets based on their biological pathways, while every biological pathway was further analysed to understand the involvement of various proteins to be targeted by the curcumin molecule.

2.3 3-D structure retrieval of the target protein

The literature studies and biological function prediction from pathways provided Mitogen-Activated Protein Kinase 3 (MAPK 3/ Erk 1), and it plays an essential role in the MAPK/ERK cascade (Garces *et al.,* 2022). They also participate in a signalling cascade activated by KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, and cytoskeletal rearrangements (Kciuk *et al.,* 2022). The MAPK/ERK cascade also initiates and regulates meiosis, mitosis, and post-mitotic functions in differentiated cells by phosphorylating several transcription factors (Kumar *et al.*, 2022). Three-dimensional structures of both proteins were downloaded from the Protein DataBank (PDB) (https://www.rcsb.org/). The Protein Data Bank (PDB) is a crystallographic database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids.

2.4 Combinatorial library construction and ligand preparations

The combinatorial library was generated for ligand library construction using two approaches: library construction through a database and another library construction approach through SimLib software.

2.4.1 Target based approach

MAP kinase 3 was searched against the chEMBL database for the ligand molecules inhibiting the targets. The molecules were downloaded and saved in SDF format. The zinc database was the approach for the target-based search. The zinc (https://zinc.docking.org/) database was queried using the protein names, and the ligand structures were downloaded in .sdf file format. The ZINC database is a curated collection of commercially available chemical compounds prepared especially for virtual screening (Bhura *et al.,* 2022).

2.4.2 Ligand based approach

The next step for the combinatorial library construction was performed using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem is a database of chemical molecules and their activities against biological assays. PubChem database was queried using “Curcumin” to search for the 3D structures. The hits with a similarity of >70% and all molecules that passed the Lipinski rule of five and were biologically active were selected for further analysis.

The second approach was performed with the chEMBL structure search option, where the curcumin structure was searched against the database with 70% similarity. Also, substructures were obtained from the curcumin substructure.

The third approach was with the ZINC database, where curcumin was searched against the database with >70% similarity. These molecules were saved in .sdf file format for further docking studies.

Natural products or ligands obtained from flora and fauna similar to curcumin were also searched through SimComp online software (https://www.genome.jp/tools/simcomp/). SIMCOMP (SIMilar COMPound) is a graph-based method for comparing chemical structures. It has been implemented in the KEGG system for searching similar chemical structures in the chemical structure databases. Similar compounds were retrieved by the global search option of curcumin structure against the KNApSAcK database (http://www.knapsackfamily.com/KNApSAcK/). The KNApSAcK package, when installed on the user's computer, provides a tool for analysingthe datasets of mass spectra that are prepared according to a particular format, as well as for retrieving information on metabolites by entering the name of a metabolite, the name of an organism, molecular weight or molecular formula. A list of metabolites associated with a taxonomic class can be obtained by searching with the taxonomic name, from which information on individual metabolites can be retrieved. PubChem also provides the patent molecules generated from the master molecules (Georrge *et al*., 2012; Patel *et al.,* 2018). These patent molecules were downloaded for combinatorial library constructions and studied to comprehend the modified groups against the master molecule curcumin.

2.4.3 Ligand library construction through SmiLib software

SMILE notations developed the combinatorial library through SmiLib software. The 3-D structure of curcumin was converted to the SMILE notation through the Marvin JS tool (https://chemaxon.com/products/marvin-js). Marvin JS is ChemAxon's novel chemical editor designed for the wider community. Marvin JS provides a clean, smart, user-oriented tool for quickly and conveniently drawing chemical structures and reactions/reaction mechanisms on web pages (Murtazalieva *et al.,* 2017). Five positions are predicted for different R group poses shown in Figure 1.

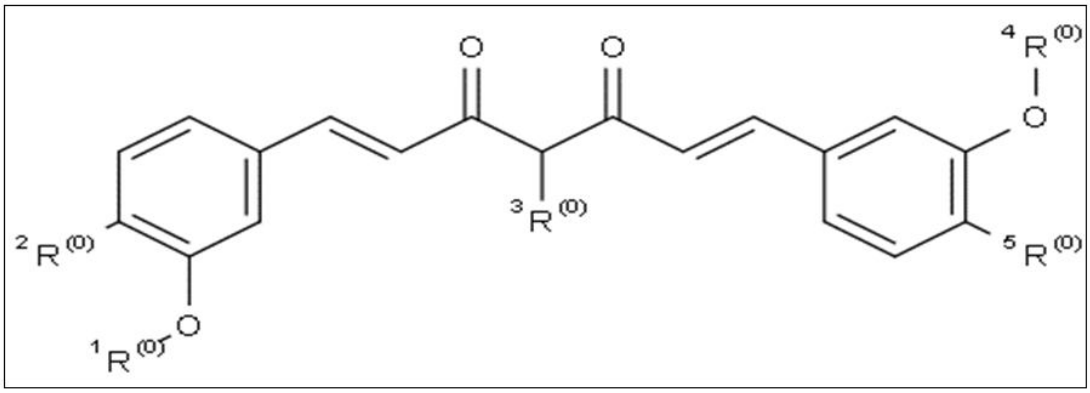


Figure 1: Different R poses for combinatorial library construction.

For every position, the SMILE notations were generated and imported into SmiLib software. SmiLib enumerates combinatorial libraries at rates of approximately 9,000,000 molecules per minute on fast computers. 95 R groups were used for all the combinations along with threeblank linkers, O and N. Combinatorial library was generated by different combinations at different positions.

Table 1: List of different R groups for combinatorial library

NAME	SMILES	NAME	SMILES
hydrogen	H	2-Piperidine	c1ncccc1
bromine	Br	3-Piperidine	c1cnccc1
chlorine	Cl	4-Piperidine	c1ccncc1
flourine	F	2-Tetrahydrothiopyran	c1scccc1
iodine	I	3-Tetrahydrothiopyran	c1csccc1
Methyl	c	4-Tetrahydrothiopyran	c1ccscc1
Ethyl	cc	2-2*H*-Pyran	c1oc=cc=c1
Propyl	ccc	3-2*H*-Pyran	c1=cc=coc1
Ethenyl	c=c	4-2*H*-Pyran	c1=ccoc=c1
Propen-3-yl or allyl	cc=c	Pyrid-2-yl	c1ncccc1
Ethynyl	c#c	Pyrid-3-yl	c1cnccc1
Prop-2-ynyl	cc#c	Pyrid-4-yl	c1ccncc1
Hydroxy	o	2-2*H*-Thiopyran	c1sc=cc=c1

Hydroxymethyl	co	3-2*H*-Thiopyran	c1=cc=csc1
Hydroxyethyl	cco	4-2*H*-Thiopyran	c1=ccsc=c1
Formyl	c=o	Cyclopentyl	c1cccc1
2-Acetaldehyde	cc=o	Cyclopenta-1,3-dienyl	c1=cc=cc1
Methoxy	oc	1-Pyrrolidine	n1cccc1
Amino	n	2-Pyrrolidine	c1nccc1
Aminomethyl	cn	3-Pyrrolidine	c1cncc1
Aminoethyl	ccn	2-Tetrahydrofuran	c1occc1
Iminomethyl	c=n	3-Tetrahydrofuran	c1cocc1
Iminoethyl	cc=n	2-Tetrahydrothiophene	c1sccc1
Cyano	c#n	3-Tetrahydrothiophene	c1cscc1
Cyanomethyl	cc#n	1-1*H*-Pyrrole	n1c=cc=c1
Mercapto	s	2-1*H*-Pyrrole	c1=cc=cn1
Mercaptomethyl	cs	3-1*H*-Pyrrole	c1=cnc=c1
Mercaptoethyl	ccs	Fur-2-yl	c1=cc=co1
Thioformyl	c=s	Fur-3-yl	c1=coc=c1
2-Thioacetaldehyde	cc=s	Thiene-2-yl	c1=cc=cs1
Carboxylic acid	c(=o)o	Thiene-3-yl	c1=csc=c1
Ethanone	c(=o)c	2-Decahydronaphthalen-2-yl	c1cc2ccccc2cc1
1-Ethenol	c(=c)o	1-Decahydronaphthalen-1-yl	c1cccc2ccccc12
Prop-1-en-2-yl	c(=c)c	2-Naphthalen-2-yl	c1ccc2ccccc2c1
Carboxamide	c(=o)n	1-Naphthalen-1-yl	cc2cccc1ccccc12
1-Ethanimine	c(=n)c	Octahydro-1*H*-inden-5-yl	c1cc2cccc2cc1
1-Ethenamine	c(=c)n	Octahydro-1*H*-inden-4-yl	c1cccc2cccc12
Carbodithioic acid	c(=s)s	Octahydro-1*H*-inden-2-yl	c1cc2ccccc2c1
1-Ethanethione	c(=s)c	Octahydro-1*H*-inden-1-yl	c1ccc2ccccc12
1-Ethenethiol	c(=c)s	1*H*-Inden-5-yl	c1cc2c=ccc2cc1
Cyclohexyl	c1ccccc1	1*H*-Inden-4-yl	c1cccc2cc=cc12
Phenyl	c1ccccc1	1*H*-Inden-2-yl	c1=cc2ccccc2c1
2-Tetrahydropyran	c1occcc1	1*H*-Inden-1-yl	c2c=cc1ccccc12
3-Tetrahydropyran	c1coccc1	Aniline	nc1ccccc1
4-Tetrahydropyran	c1ccocc1	Ethyl propanoate	ccc(=o)occ
1-Piperidine	n1ccccc1	Nitrogen trifluoride	n(f)(f)f
Methoxymethanol	coco	Trifluoro-methanol	oc(f)(f)f
		2-ethoxyethanol	ccocco

2.5 Protein-ligand docking

The biologically active protein MAP kinase 3 was screened for protein-ligand docking with the combinatorial ligand library.

2.5.1 Ligand preparation

The combinatorial library created was divided into two sets, where Set1 consisted of the chemical ligands retrieved through target-based and ligand-based approaches. In contrast, Set2 consisted ofall the natural product molecules obtained from different plants. Molecules generated were prepared by using the LigPrep module of Schrodinger. LigPrep is an efficient program capable of generating ligand libraries, including tautomeric and ionisation states, ring confirmations and stereoisomerism, reducing bond errors (Mohan *et al.,* 2022).

2.5.2 Drug likeliness property prediction using QikProp

QikProp rapidly screens compounds by predicting the widest variety of relevant properties such as Log P, HERG, MDCK, Rule

of 5 and many more (Obadawo *et al.,* 2022). Before HTVS, all the drug-likeliness properties of molecules were predicted accurately. Molecules passing QikProp properties were exported and taken for further confirmed docking against target proteins.

2.5.3 Protein preparations

X-ray crystal structure of protein MAP kinase 3 were downloaded from the RCSB Protein DataBank (PDB) (https://www.rcsb.org/) database and were prepared using protein preparation wizard, as the protein from PDB may contain missing atoms or co-crystallised ligands, water molecules, cofactor molecules or even metal ions. Therefore, this is a prerequisite step (Pietruœ *et al.,* 2022).

2.5.4 Glide grid preparation

Glide offers a full spectrum of high throughput binding mode predictions. Receptor grids were calculated after protein preparation so that the best ligand pose could bind properly into the active site during docking. Active site amino acid residues for both proteins were found from literature studies and through the labels module of Molegro virtual docker (MVD) and imported while grid preparations(Gentile *et al.,* 2022).

2.5.5 High throughput virtual screening (HTVS) docking

Docking was carried out for all three ligand sets generated by two ways of combinatorial library generation after LigPrep against both the proteins separately using the HTVS mode of Glide in Schrodinger, one of the best methods to identify and rank potential drug candidates.

2.5.6 XP ligand docking

The top 200 molecules with the lowest docking scores screened from HTVS were further docked using the XP module of Glide in Schrodinger. XP Glide methodology is to semi-quantitatively rank the ability of candidate ligands to bind to a specified conformation of the protein receptor (Mateev *et al.,* 2022). These results were further compared with master molecules that are curcumin, its derivatives and approved drugs for the target proteins.

3. Results

3.1 Biological function prediction

Biological function prediction was carried out for the target and ligand through databases such as UniProt, KEGG, chEMBL, PubChem and literature studies. All these databases' results were compared to find common targets and drugs. Finally, Mitogen-Activated Protein Kinase 3 (MAPK 3) were selected from biological pathways, and the structure representation is shown in Figure 2. MAP kinase 3 are involved in many pathways from the classification studies using the KEGG pathway database (Dasgupta *et al.,* 2020; Kanehisa *et al.,* 2019; Sinkala *et al.,* 2021). MAPKs are expressed one-third times higher in cancerous cells compared to normal situations. Regulating these protein productions can cure multiple diseases (Braicu *et al.,* 2019).

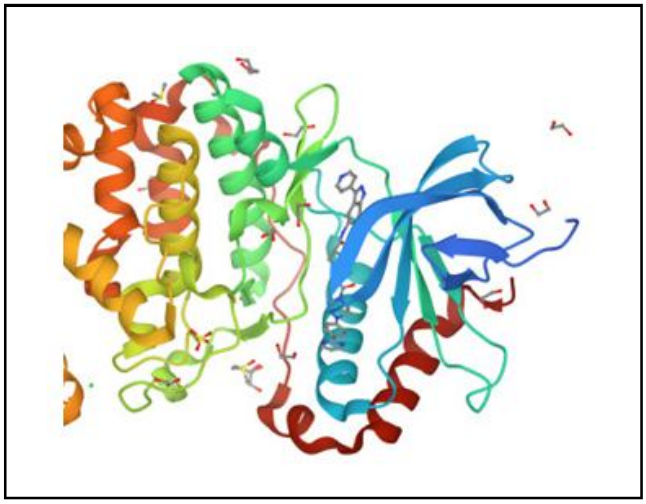


Figure 2: Structure representation of MAP Kinase 3 (PDB Id: 4QTB).

3.2 Combinatorial library generation

A combinatorial library created through three approaches generated several similar molecules to curcumin. In the target-based approach, 749 molecules were retrieved chEMBL, and ten molecules were retrieved from the ZINC database of MAPK 3. In the ligand-based approach, curcumin structure was searched against the database for the similar compound, where PubChem provided 1433 hits, chEMBL with 220 hits and ZINC database with 395 similar molecules. SimComp search for natural products against the KNApSAck database provided 300 similar compounds and 250 patented analogues retrieved from the PubChem database. SmiLib Software used for combinatorial library generation created 285 molecules for every R group position; 95 functional groups were predicted along with three different linkers; blank, N and O. Therefore, 1425 ligands were generated through SmiLib, as shown in Table 2.

Table 2: Combinatorial library generations through different approaches

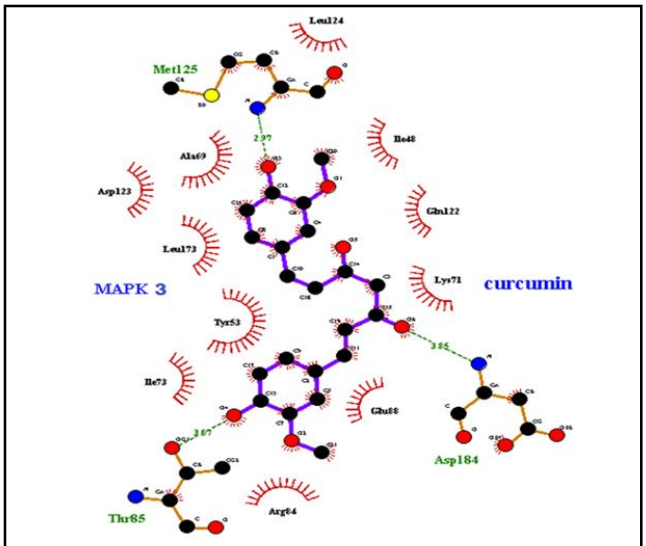
Combinatorial library	No. of molecules	Total number
Target aased approach		
chEMBL (MAPK 3)	749	759
ZINC database (MAPK 3)	10	
Ligand based approach		
PubChem	1433	2048
chEMBL	220	
ZINC database	395	
Natural products		
KNApSAcK	300	300
Patent Molecules	250	250
SmiLib software	1425	**1425**

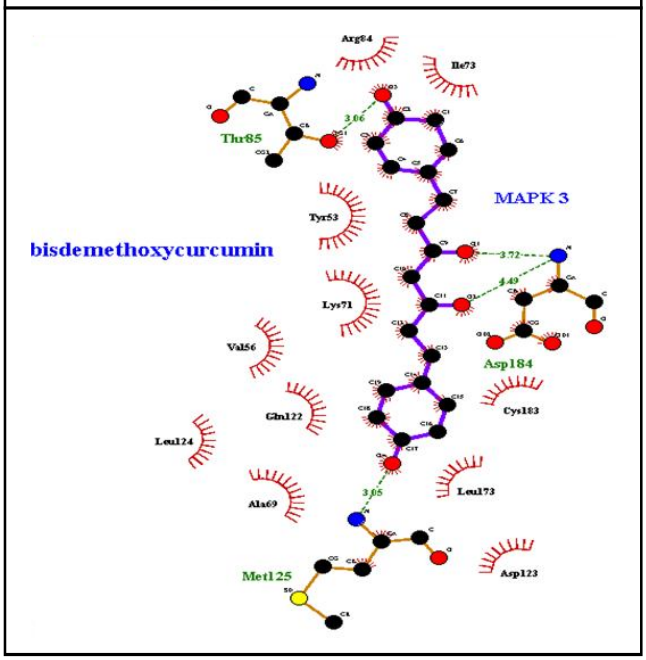
3.3 Docking analysis of targets

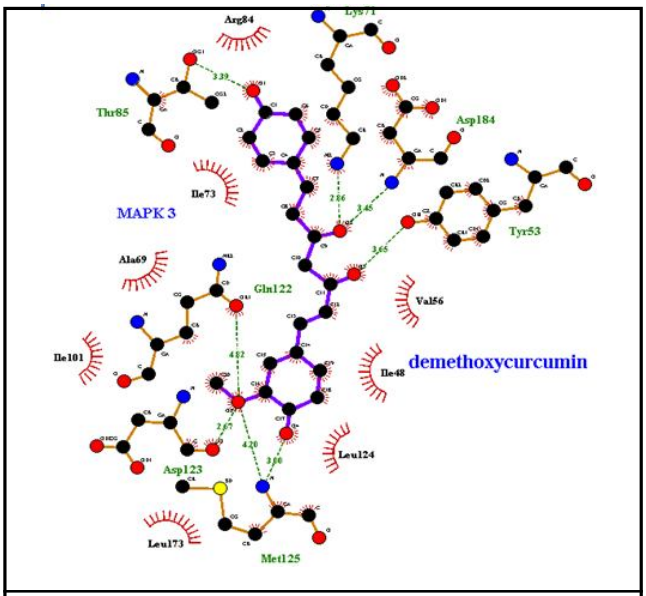
3D structures of curcumin and its derivatives and Sulindac-approved drug for Erk1 were obtained, and docking with both proteins was performed. These molecules were considered the master molecules, and docking results were analysed, referenced to these docking results in Table 3 and docked complex of different targets with the MAPK3 is shown in Figure 3.

Table 3: Docking results of curcumin, its derivatives and approved drugs

Ligand name	Docking score (kcal)
Curcumin	-9.550021
Bisdemethoxy curcumin	-7.455148
Demethoxy curcumin	-7.126899
Approved drug (sulindac)	-5.025903







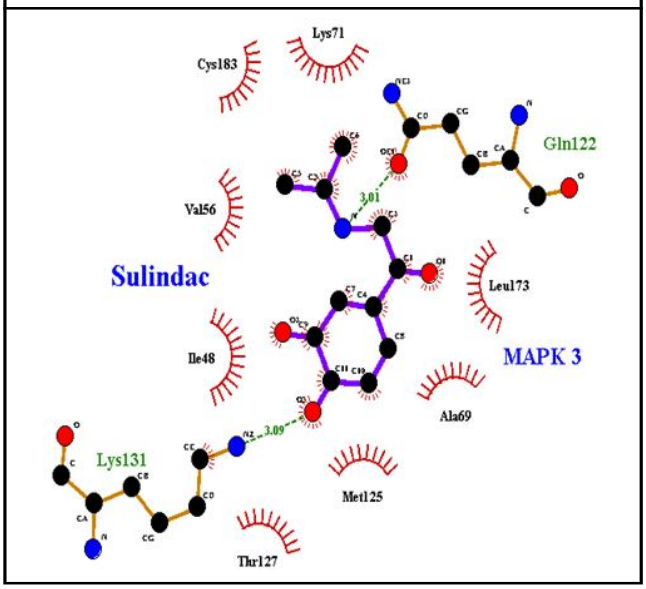


Figure 3: Interactions of derivatives and approved drugs with MAPK 3.

Curcumin is found to be the most active component of turmeric than its derivatives. The docking results values (Table 3) show the highest interaction of curcumin with MAPK 3 compared to its derivatives, and interactions (Figure 3) show the highest residues interaction where curcumin forms hydrogen bonds with methionine, aspartic acid and threonine. Besides curcumin, its derivatives include hydrogen bonds with tyrosine, lysine, glutamine and arginine. With all the above compounds generated, docking was performed using Schrodinger to obtain better results. Docking results with the least energy value compounds for both proteins from both libraries are shown below. The XP docking results of combinatorial library molecules where the top 10 selected molecules show the better results compared to curcuminare shown in Table 4, from which CHEMBL2420897 show good binding with the ERK1 and these interactions of CHEMBL2420897 shown in Figure 4. And the docked complex also shows the hydrogen bond interactions with the proteins MAPK3.

Table 4: Docking results of chemical molecules from chEMBL, ZINCdb and PubChem

Serial No.	ID	Docking score (Kcal)
1.	CHEMBL2420897	-9.843609
2.	CHEMBL2325894	-8.197869
3.	CHEMBL2325905	-9.553246
4.	CHEMBL2420907	-8.649667
5.	CHEMBL2325894	-7.717144
6.	CHEMBL2325905	-9.286412
7.	90959022	-9.242155
8.	57087097	-9.186392
9.	CHEMBL243931	-9.197652
10.	ZINC02170223	-9.186395

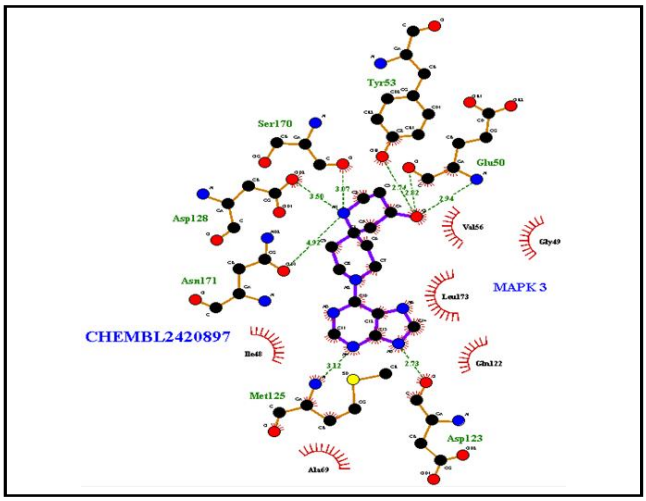


Figure 4: Interaction of CHEMBL2420897 with MAPK 3.

Docking results (Table 4) of chemical compounds similar to the curcumin molecules show a better binding ratio than the master molecule with the proteins. Interactions (Figure 4) of the CHEMBL2420897 molecule show more hydrogen bonds formed with residues asparagine, arginine, aspartic acid, serine, and methionine as the molecule consists of higher O and H atoms to form a hydrogen bond.The Docking results of natural product molecules C00005110 and C00010263 from the KNApSAcK database show the highest interaction highlighted in Table 5 and Figure 5.

Table 5: Docking results of natural product molecules from the KNApSAcK database

Serial No.	ID	Docking score (kcal)
1.	C00005110	-8.103945
2.	C00010263	-9.704173
3.	C00038101	-9.429353
4.	C00000653	-9.054141
5.	C00038321	-7.906258
6.	C00007207	-6.78218
7.	C00043617	-9.040253
8.	C00005503	-8.861099
9.	C00007203	-8.956322
10.	C00007200	-8.113135

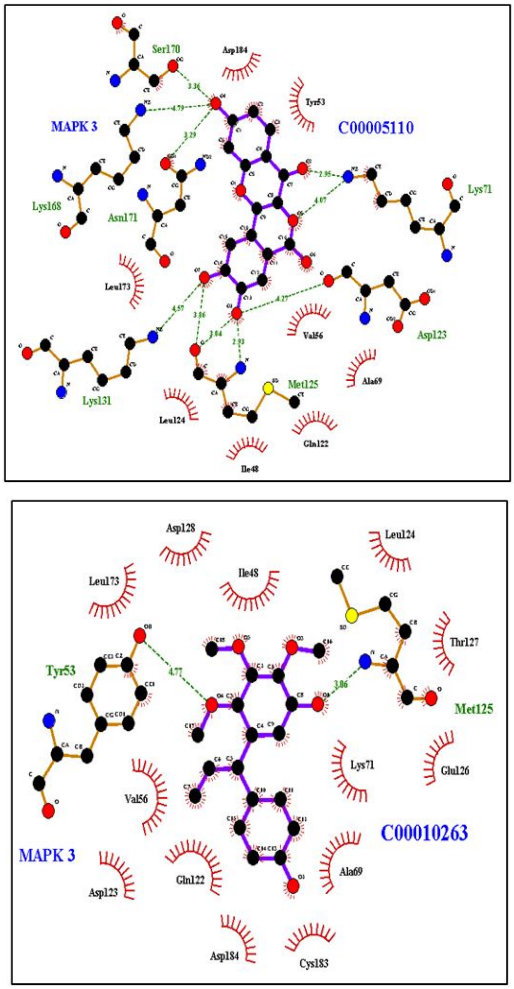


Figure 5: Interactions of C00005110 and C00010263 with MAPK 3.

Natural product C00010263 Kuhlmanniquinol and C00005110 Fasciculiferin shows the highest in teraction ratio compared to other similar molecules of curcumin (Table 5); these molecules have higher interactions hydrogen binding with the O atoms to residues lysine, tyrosine and methionine. Docking results of patent molecules from PubChem database 68553355 and 51042421 show the highest interaction highlighted in Table 6 and Figure 6.

Table 6: Docking results of patent molecules from PubChem database

Serial No.	ID	Docking score (kcal)
1	68553355	-10.214367
2	51042421	-9.236893
3	68555728	-9.913763
4	78200755	-9.816413
5	21338011	-8.558815
6	68553901	-9.548684
7	91809441	-9.505553
8	68555092	-9.499864
9	68550021	-7.090721
10	68556090	-9.228538

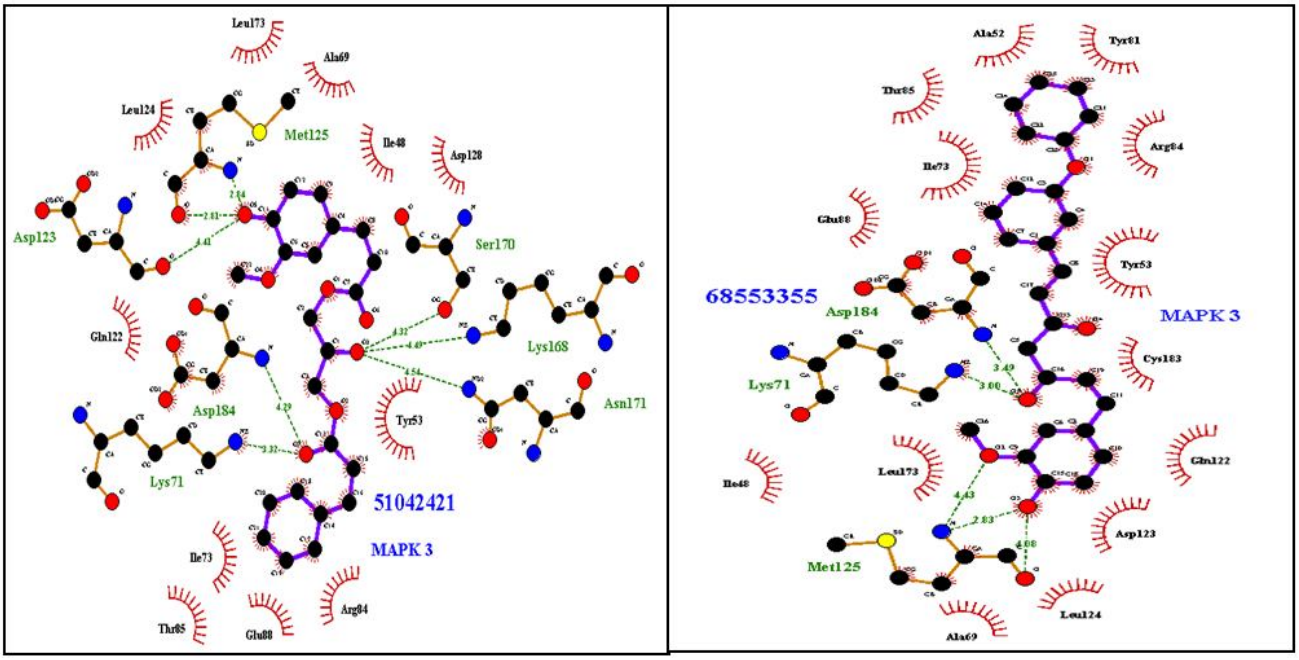


Figure 6: Interactions of 51042421 and 68553355 patent molecule with MAPK 3.

Patent molecules are modified from the carbon backbone chain and 5th position of the R group by adding oxygen atoms. A higher number of O atoms forms a higher hydrogen bond with MAPK 3 (Figure 6). The addition of oxygen atoms increases interactions with proteins, showing higher docking values compared to curcumin and its derivatives (Table 6). Docking results of the combinatorial library from SmiLib software in which ID 1.1.57 shows the highest interaction are highlighted in Table 7 and Figure 7.

Table 7: Docking results of the combinatorial library from SmiLib software

Serial No.	ID	Docking score (kcal)
1.	1.1_57	-10.385853
2.	1.3_6	-8.358383
3.	1.3_38	-9.276886
4.	1.3_33	-8.152181
5.	1.1_73	-9.963454
6.	1.3_60	-9.029382
7.	1.2_73	-9.638325
8.	1.1_90	-9.606634
9.	1.3_59	-6.641937
10.	1.1_14	-9.449644
11.	1.1_15	-8.740927
12.	1.3_26	-8.496524
13.	1.3_62	-9.564933

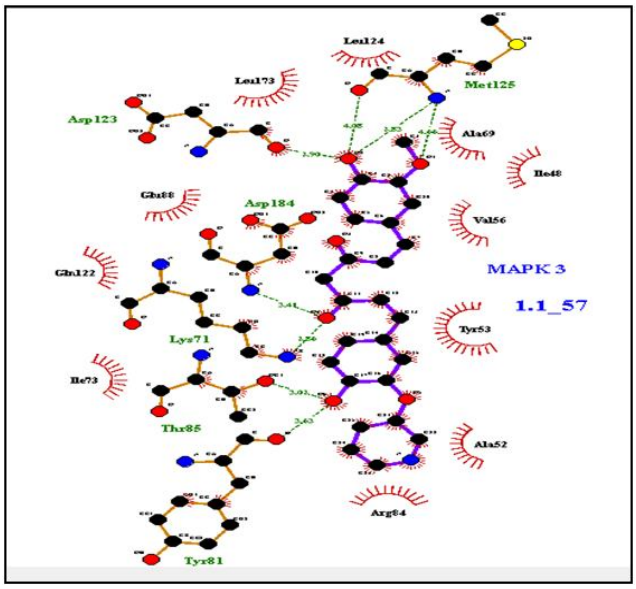


Figure 7: Interactions of molecule generated from SmiLib software.

Structures generated from SmiLib software were modified from 5 different positions by changing functional groups. Docking results of these molecules were found to show the best results compared to curcumin, its derivatives, approved drugs and ligand libraries from the database. In some way, the best result increases the interactions with MAPK 3. The interaction shows the higher hydrogen bond interactions with residues methionine, tyrosine, Threonine and aspartic acid (Figure 7). Also, the modified regions containing O atoms are found to be active in hydrogen bonding with the proteins.

4. Discussion

Turmeric (*C. longa*) is a medicinal plant that has different bioactive compounds and is widely used in treating several diseases such as anticancer, antiviral, antiarthritic, antiamyloid, antioxidant, and anti-inflammatory properties and also used as a common Indian spice in the form of turmeric because of their several health benefits. Several studies found that *C. longa* can be essential in combating several diseases. As seen in the current scenario, turmeric (*C. longa*) was widely used against COVID-19 to increase the immune system response. Although, the different derivatives curcumin, bisdemethoxycurcumin and desmethoxycurcumin also have different bioactive that are widely used worldwide, especially in India. So in this study, with the help of an advanced computational tool, the analogue molecules are constructed with database search and the SmiLib combinatorial library approach to provide a novel drug molecule targeting MAPKs (ERK1). Mitogen-activated protein kinase (MAPK) is thought to regulate different cell survival and apoptosis mechanism and is also widely expressed with different signalling. Based on that, finding novel molecules against Mitogen-activated protein kinase (MAPK) can cure multiple diseases. SmiLib Software used for combinatorial library generation created 285 molecules for every R group position; 95 functional groups (Table 1) were predicted along with three different linkers, blank, N and O, and a combinatorial library created through three approaches (Target Based Approach, Ligand Based Approach, Natural Products) generated several similar molecules to curcumin as shown in Table 2. Further, the docking analysis between the MAPK3 with curcumin, its derivatives and approved drugs shows successful binding interaction based on the obtained docking score (Table 3) and found that among them, curcumin shows the highest interaction with the MAPK3. Also, the docking analysis between the chemical molecules' natural product molecules, patent molecules and molecules generated through the combinatorial library from SmiLib software with MAPK3 shows a significant binding interaction. This complete analysis found that the few natural products and molecules generated through the SmiLib approach provide better docking results and hydrogen bond interactions with MAPK 3 proteins, promising to develop into drug molecules for multiple biological targets.

5. Conclusion

For thousands of years, curcumin has been used in the Orient as a healing agent for many inflammatory, neoplastic and other conditions. The great therapeutic potential against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases, and HIV, has been documented in recent years. According to PubMed(https://pubmed.ncbi.nlm.nih.gov/), more than 20,000 studies have been conducted with curcumin to find the different aspects for better outcomes. This natural product can modulate multiple cellular signalling pathways and affect numerous molecular targets. Although, curcumin is relatively safe in humans, its low bioavailability may be a limitation for clinical use. Various approaches are being undertaken to enhance the bioavailability of curcumin. More studies are needed to evaluate the efficacy and the safety of reformulated curcumin fully, the structural analogues of curcumin, and the combination of curcumin with existing therapies.

Nevertheless, the low cost, pharmacological safety, proven therapeutic efficacy and multiple targeting potential make curcumin a promising agent for the prevention and treatment of various human diseases. Meanwhile, this research has provided curcumin reformulations with enhanced molecule bioavailability compared to curcumin and its derivatives. Few natural products and molecules generated through the SmiLib approach provide better docking results and hydrogen bond interactions with MAPK 3 proteins, promising to develop into drug molecules for multiple biological targets. MAPKs are proteins found to be involved in many diseased pathways. Apart from the available patented molecules, the SmiLib-generated molecules provided better results than others. Hence, regulations of these proteins through the further generation of new combinations of molecules,with the help of a better computational approach,can provide a novel drug molecule to cure multiple diseases.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

Authors' contributions

Vakhariya Sakina S. and Saurav Kumar Mishra are joint first authors. Vakhariya Sakina S., Saurav Kumar Mishra, and Kanchan Sharma contributed to the study conception and design, data acquisition, analysis, interpretation of data, and manuscript drafting. John J. Georrge contributed to the analysis and interpretation of data and critical revision. All authors have approved the final version for submission.

References

Alrawaiq, N. S. and Abdullah, A. (2014). A review of antioxidant polyphenol curcumin and its role in detoxification. Int. J. Pharm. Tech. Res., **6**:280-289.

Bhura, N.; Gupta, P. and Gupta, J. (2022). Target-based *in silico* screening of basil polysaccharides against different epigenetic targets responsible for breast cancer. Journal of Receptors and Signal Transduction, **42**:521-530. https://doi.org/10.1080/10799893. 2022.2058016.

Braicu, C.; Buse, M.; Busuioc, C.; Drula, R.; Gulei, D.; Raduly, L.; Rusu, A.; Irimie, A.; Atanasov, A. G.; Slaby, O.; Ionescu, C. and Berindan-Neagoe, I. (2019). A comprehensive review on MAPK: A promising therapeutic target in cancer. Cancers (Basel),**11**:1618. https://doi.org/10.3390/cancers11101618.

Dasgupta, P.; Kulkarni, P.; Bhat, N. S.; Majid, S.; Shiina, M.; Shahryari, V.; Yamamura, S.; Tanaka, Y.; Gupta, R. K. and Dahiya, R. (2020). Activation of the Erk/MAPK signaling pathway is a driver for cadmium induced prostate cancer. Toxicology and Applied Pharmacology, **401**:115102. https://doi.org/10.1016/j.taap.2020.115102.

Dusabumuremyi, J. C.; Duhoranimana, E. and Chen, X. (2022). Health benefits of turmeric and ginger. Handbook of Nutraceuticals and Natural Products: Biological, Medicinal, and Nutritional Properties and Applications,**2**:259-268. https://doi.org/10.1002/9781119746843.ch24.

Garces, S.; Medeiros, L. J.; Marques-Piubelli, M. L.; Siqueira, S. A. C.; Miranda, R. N.; Cuglievan, B.; Sriganeshan, V.; Medina, A. M.; Garces, J. C. and Saluja, K. (2022). Cyclin D1 expression in Rosai-Dorfman disease: A near-constant finding that is not invariably associated with mitogen-activated protein kinase/extracellular signal-regulated kinase pathway activation. Human Pathology, **121**:36-45. https://doi.org/10.1016/j.humpath.2021.12.013.

Gentile, F.; Yaacoub, J. C.; Gleave, J.; Fernandez, M.; Ton, A.-T.; Ban, F.; Stern, A. and Cherkasov, A. (2022). Artificial intelligence-enabled virtual screening of ultra-large chemical libraries with deep docking. Nature Protocols, **17**:672-697. https://doi.org/10.1038/s41596-021-00659-2

Georrge, J. J. and Umrania, V. (2012). Subtractive genomics approach to identify putative drug targets and identification of drug-like molecules for beta subunit of DNA polymerase III in Streptococcus species. Applied Biochemistry and Biotechnology, **167**:1377-1395.https://doi.org/10.1007/s12010-012-9620-0.

Guo, Y. J.; Pan, W. W.; Liu, S. B.; Shen, Z. F.; Xu, Y. and Hu, L. L. (2020). ERK/MAPK signalling pathway and tumorigenesis. Exp. Ther. Med., **19**:1997-2007. https://doi.org/10.3892/etm.2020.8454.

Hadi, J.; Wu, S. and Brightwell, G. (2020). Antimicrobial blue light versus pathogenic bacteria: Mechanism, application in the food industry, hurdle technologies and potential resistance. Foods, **9**:1895. https://doi.org/10.3390/foods9121895.

Haftcheshmeh, S. M.; Mirhafez, S. R.; Abedi, M.; Heydarlou, H.; Shakeri, A.; Mohammadi, A. and Sahebkar, A. (2022). Therapeutic potency of curcumin for allergic diseases: A focus on immunomodulatory actions. Biomedicine and Pharmacotherapy,**154**:113646. https://doi.org/10.1016/j.biopha.2022.113646.

Hidayat, R. and Wulandari, P. (2022). Potency of turmeric (*Curcuma longa* L.) and temulawak (*Curcuma xanthorrhiza* Roxb.) in handling coronavirus disease 2019 (COVID-19). Eureka Herba Indonesia, **3**:140-143. https://doi.org/10.37275/ehi.v3i2.57.

Howes, M.-J. R. (2018). Phytochemicals as anti-inflammatory nutraceuticals and phytopharmaceuticals. In: Immunity and Inflammation in Health and Disease, pp:363-388. https://doi.org/10.1016/B978-0-12-805417-8.00028-7.

Kanehisa, M.; Sato, Y.; Furumichi, M.; Morishima, K. and Tanabe, M. (2019). New approach for understanding genome variations in KEGG. Nucleic Acids Research, **47**:D590-D595. https://doi.org/10.1093/nar/gky962.

Karak, P. and Modak, A. (2022). Curcumin and its anticancer properties: kitchen to the laboratory. Indian Journal of Physiology and Allied Sciences, **74**:13-18. https://ijpas.org/index.php/ijpas/article/view/51.

Kciuk, M.; Gieleciñska, A.; Budzinska, A.; Mojzych, M. and Kontek, R. (2022). Metastasis and MAPK pathways. International Journal of Molecular Sciences, **23**:3847. https://doi.org/10.3390/ijms23073847.

Kotadiya, R. and Georrge, J. J. (2015). 1. *In silico* approach to identify putative drugs from natural products for Human Papillomavirus (HPV) which cause cervical cancer. Life Sciences Leaflets, **62**:1 to 13-11 to 13.

Kumar, D. and Hassan, M. I. (2022). Recent advances in the therapeutic development of ERK inhibitors. Protein Kinase Inhibitors, pp:129-178. https://doi.org/10.1016/B978-0-323-91287-7.00023-5.

Liang, Z.; Wu, R.; Xie, W.; Zhu, M.; Xie, C.; Li, X.; Zhu, J.; Zhu, W.; Wu, J.; Geng, S.; Xu, W.; Zhong, C. and Han, H. (2018). Curcumin reverses tobacco smokeinduced epithelialmesenchymal transition by suppressing the MAPK pathway in the lungs of mice. Mol. Med. Rep., **17**:2019-2025. https://doi.org/10.3892/mmr.2017.8028.

Liu, S.; Liu, J.; He, L.; Liu, L.; Cheng, B.; Zhou, F.; Cao, D. and He, Y. (2022). A comprehensive review on the benefits and problems of curcumin with respect to human health. Molecules, **27**:4400. https://doi.org/10.3390/molecules27144400.

Lo Cascio, F.; Marzullo, P.; Kayed, R. and Palumbo Piccionello, A. (2021). Curcumin as Scaffold for drug discovery against neurodegenerative diseases. Biomedicines, **9**:173. https://doi.org/10.3390/Biomedicines 9020173.

Mateev, E.; Georgieva, M. and Zlatkov, A. (2022). Improved molecular Docking of MAO-B Inhibitors with glide. Biointerface Research in Applied Chemistry, **13**:159. https://doi.org/10.33263/BRIAC132.159.

Mohan, A.; Schwenk, G.; Jeeva, A.; Feng, E. and Ji, H.-F. (2022). Pharmacophore based virtual screening for identification of effective inhibitors to compact HPV 16 E6 a triggered cervical cancer. https://doi.org/10.21203/rs.3.rs-1996595/v1.

Murtazalieva, K.; Druzhilovskiy, D.; Goel, R.; Sastry, G. and Poroikov, V. (2017). How good are publicly available web services that predict bioactivity profiles for drug repurposing? SAR and QSAR in Environmental Research, **28**:843-862. https://doi.org/10.1080/1062936X.2017.1399448.

Obadawo, B. S.; Oyeneyin, O. E.; Owolabi, T. O.; Metibemu, D. S.; Ipinloju, N.; Fagbohungbe, K. H.; Modamori, H. O. and Olatoye, V. O. (2022). Investigation of the anticancer potential of 2-alkoxycarbonylallyl esters against metastatic murine breast cancer line 4T1 targeting the EGFR: A combined molecular docking, QSAR, and machine learning approach. Letters in Drug Design and Discovery,**19**:1068-1085. https://doi.org/10.2174/1570180819666220512111613.

Panda, S.; Swain, S. K.; Sahu, B. P. and Sarangi, R. (2022). Gene expression and involvement of signaling pathways during host–pathogen interplay in *Orientia tsutsugamushi* infection. 3 Biotech, **12**:1-14. https://doi.org/10.1007/s13205-022-03239-7.

Patel, C. N.; Georrge, J. J.; Modi, K. M.; Narechania, M. B.; Patel, D. P.; Gonzalez, F. J. and Pandya, H. A. (2018). Pharmacophore-based virtual screening of catechol-o-methyltransferase (COMT) inhibitors to combat Alzheimer's disease. Journal of Biomolecular Structure and Dynamics, **36**:3938-3957.https://doi.org/10.1080/07391102.2017.1404931.

Pietruœ, W.; Kafel, R.; Bojarski, A. J. and Kurczab, R. (2022). Hydrogen bonds with fluorine in ligand–protein complexes-the PDB analysis and energy calculations. Molecules, **27**:1005. https://doi.org/10.3390/molecules27031005.

Purushothaman, A.; Rose, K. T.; Jacob, J. M.; Varatharaj, R.; Shashikala, K. and Janardanan, D. (2022). Curcumin analogues with improved antioxidant properties: A theoretical exploration. Food Chemistry, **373**:131499. https://doi.org/10.1016/j.foodchem.2021.131499

Rajagopal, K.; Varakumar, P.; Baliwada, A. and Byran, G. (2020). Activity of phytochemical constituents of *Curcuma longa* (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19): An in silico approach. Futur. J. Pharm. Sci., **6**:1-10. https://doi.org/10.1186/s43094-020-00126-x

Ronkina, N. and Gaestel, M. (2022). MAPK-activated protein kinases: Servant or partner? Annual Review of Biochemistry, **91**:505-540.https://doi.org/10.1146/annurev-biochem-081720-114505

Sharifi-Rad, J.; Rayess, Y. E.; Rizk, A. A.; Sadaka, C.; Zgheib, R.; Zam, W.; Sestito, S.; Rapposelli, S.; Neffe-Skocinska, K.; Zielinska, D.; Salehi, B.; Setzer, W. N.; Dosoky, N. S.; Taheri, Y.; El Beyrouthy, M.; Martorell, M.; Ostrander, E. A.; Suleria, H. A. R.; Cho, W. C.; Maroyi, A. and Martins, N. (2020). Turmeric and its major compound curcumin on health: Bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Front. Pharmacol., **11**:01021. https://doi.org/10.3389/fphar.2020.01021.

Simu, S. Y.; Alam, M. B. and Kim, S. Y. (2022). The activation of Nrf2/HO-1 by 8-Epi-7-deoxyloganic acid attenuates inflammatory Symptoms through the Suppression of the MAPK/NF-κB Signaling Cascade in *in vitro* and *in vivo* Models. Antioxidants,**11**: 1765. https://doi.org/10.3390/antiox11091765.

Sinkala, M.; Nkhoma, P.; Mulder, N. and Martin, D. P. (2021). Integrated molecular characterisation of the MAPK pathways in human cancers reveals pharmacologically vulnerable mutations and gene dependencies. Commun. Biol.,**4**:1-16. https://doi.org/10.1038/s42003-020-01552-6

Tambawala, H.; Batra, S.; Shirapure, Y. and More, A. P. (2022). Curcumin-A biobased precursor for amart and active food packaging systems: A review. Journal of Polymers and the Environment, **30**:2177-2208. https://doi.org/10.1007/s10924-022-02372.

Vakhariya Sakina, S. and Georrge, J. J. (2016). Curcumin: A multi-tasking molecule. Proceedings of 9th National Level Science Symposium on Recent Trends in Science and Technology (ISBN 97881929 52123), **3**: 272.

Yuan, J.; Dong, X.; Yap, J. and Hu, J. (2020). The MAPK and AMPK signalings: Interplay and implication in targeted cancer therapy. J. Hematol. Oncol.,**13**:113. https://doi.org/10.1186/s13045-020-00949-4

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