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Original Research Article

Harnessing the potential of ginger/derivatives as therapeutic targets in the management of knee osteoarthritis: a molecular docking approach

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ABSTRACT

Background: Amongst musculoskeletal diseases, knee osteoarthritis (KOA) form most critical chronic joint disorder being more prevalent in females than in males, increases markedly in elderly population and correlate significantly with obesity. The structural alterations underlining KOA includes cartilage degradation, subchondral bone lesion, osteophyte formation, and altered changes in synovium and joints capsule.Inflammation forms core player of KOA to set in progressive and degenerative changes of knee joints vis-a-vis up regulate battery of pro-inflammatory cytokines including (TNF-α,IL-1β) as well as inflammasome complex(NLRP3).We hypothesize that ginger/its derivatives which have been well documented for their culinary and anti-inflammatory functions would be effective as anti-inflammatory in KOA to protect the joint degeneration.
Methods: In the present study we selected 15 ginger derivatives (literature survey) and with molecular docking approach screened the derivatives targeted against potent key inflammatory markers of KOA including TNF-α, IL-1β and inflammasome NLRP3complex. Subsequently we scored for highest binding energy and lowest binding distance (HBE-LBD) using Schrödinger software.
Results: Interestingly, we show that 6-gingerol and Zingerone demonstrated highest HBE-LBD for TNF-α,6-gingerol and paradol for IL-1β, and 8-gingerol and 10-gingerol for NLRP3 receptor.
Conclusions: Our findings are novel and report for the first time for the differential cross talk of ginger derivatives for a given Ligand displaying higher binding affinity and specificity to inflammatory targets. Way forward, we advocate carrying out efficacy studies using combinational approach 6-gingerol/Zingerone/paradol vis-à-vis 8-gingerol and 10-gingerol in KOA model to unravel target precision of the identified ginger derivatives so as to arrive for their therapeutic signatures in management of KOA.

Keywords: Musculoskeletal diseases, Knee osteoarthritis, Zinger derivatives, 6-Gingerol, 8- Gingerol, Inflammation, TNF-α - IL-1β and inflammasome NLRP3

INTRODUCTION

Musculoskeletal (MSK) diseases form huge proportion across the globe (approximately 1.63 billion) resulting in disability and degeneration as osteoarthritis, rheumatoid arthritis fractures, amputation, presentation of severe pain in lower back, neck , as well as sports related injuries etc.[1] In fact, past three decades there has been a steep rise across the globe in KOA from 247.51 million (1990) to 527.81 million (2019) with an increase in prevalence reported in females (317.44 million) against males (210.37 million) as well as age dependent increase (> 60) to coin MSK as

socioeconomic burden and of public health concerns.[2,3] KOA depicts chronic low-grade inflammation with significant degenerative changes in knee joints vis a vis complemented by imaging and diagnostic techniques.[4] Of great concerns have been the participation of inflammatory pathways (IL-β,TNF-α,IL-6 etc.) and their cross talk downstream with inflammasome complex/NLRP3 consisting of a nucleotide-binding protein and oligomerization domain-like receptor NLRP3.[5-7] Studies show that NLRP3 activation is a complex and cascade event with a plethora of multiple mediators participating to cause oligomerization of inflammasome.[8] The cascade results in activation of IL-1β, TNF-α and IL-18 inflammatory biomarkers[9] (Graphical abstract) to enhance transcription of NFkB and activator protein-1 (AP-1) resulting in chondrocyte and synoviocytes death as well as increased expression of MMP-13 and aggrecanases (ADAMTS-4 and 5) targeting the cartilage degeneration.[8,9]

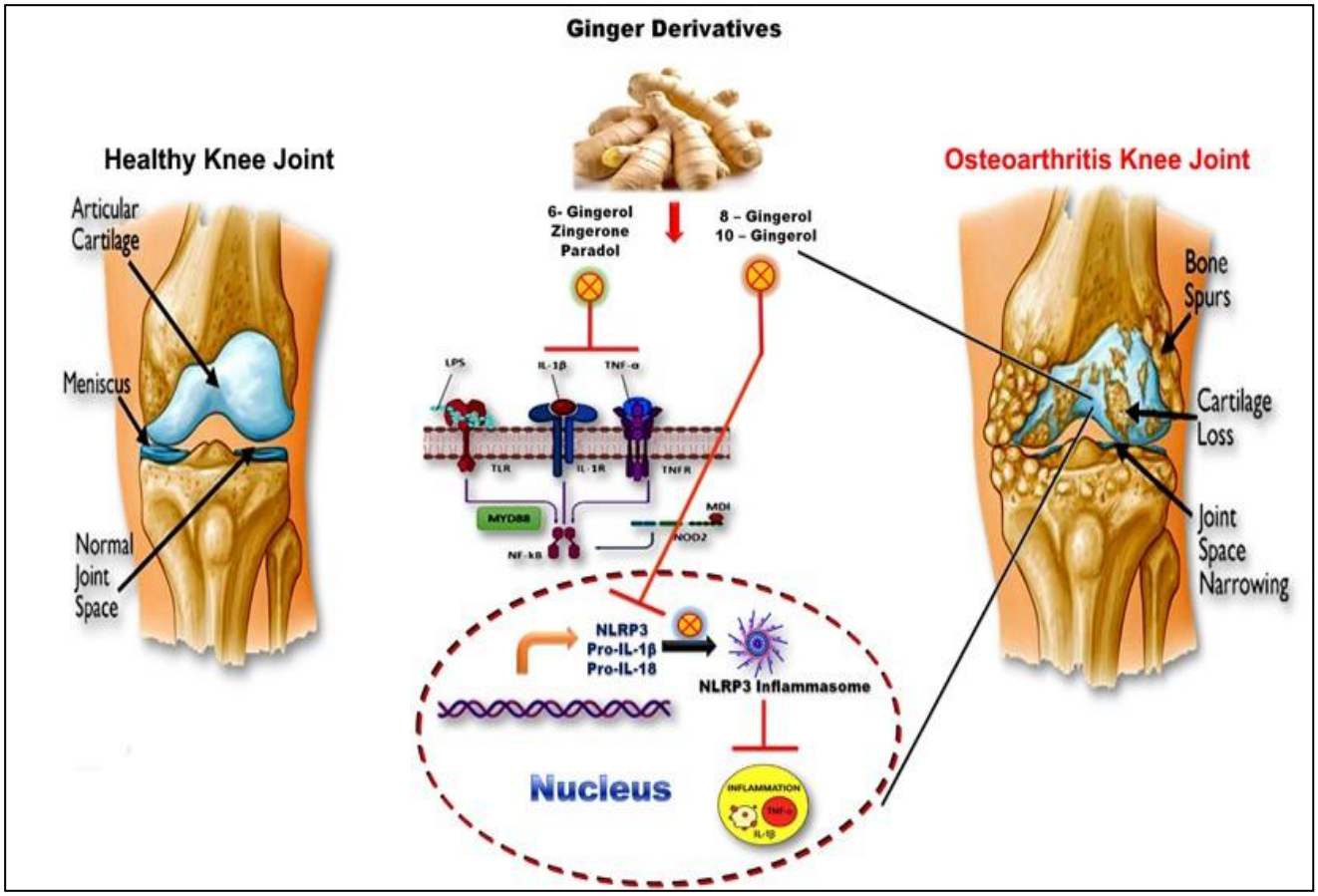

Figure 1: Schematic representation of the dynamic regulation by the ginger derivatives to avert inflammation in KOA.[10,11]

Several approaches have been in the forefront as therapeutic option of KOA[12,13] nevertheless, long-term efficacy has not been clearly understood.[14] Indeed, in recent years, plant-based derivatives and nutraceuticals have gained greater awareness in the management of diseases including KOA owing to their inherent antioxidant, anti-inflammatory and immunomodulatory functions. Of utmost medicinal value has been Ginger family (Zingiber officinale), a commonly used spice which contains non-volatile oleoresin emitting characteristic pungency/volatile essential oils (sesquiterpenes) and oleoresin constituting key physiologically active substance(s) (gingerols, shogaols, paradols, and zingerone etc.).[15] Studies *in vitro* using cultured human and SW1353 cell cultures have unequivocally demonstrated for anti-inflammatory effects of ginger extracts in synoviocytes against IL-1β, TNF-α, COX-2 /chemokines MCP-1 and IP-10 and cartilage destruction by zingerone against p38 and JNK by MMP-13.[16,17] In corroboration supporting findings by preclinical data in KOA, ginger extracts negated the effects of MMP-13 and way forward beneficial effects of oral ginger extracts showed decreased joint pain with reduced inflammation which were exemplified with serum level of, TNF-α and IL-1β, as well as their potent topical gel applications to reduce knee pain in KOA patients.[18-20]

Although, the efficacy and beneficial effects of ginger extracts have been documented, it necessitates understanding the molecular interaction(s) vis-à-vis crosstalk between ginger derivatives versus key inflammatory markers predominant in KOA to pin down them as therapeutic targets. The object of the present study was to evaluate the binding interactions of fifteen ginger-

derivatives (literature survey) using an *in-silico* and molecular docking approach. We studied their interactions so as to arrive for highest binding energy and lowest binding distance (HBE-LBD) with pro-inflammatory markers TNF-α, IL-1β, and the NLRP3 inflammasome using Biovia and Schrödinger software to get precise and specific interactions.

METHODS

Preparation of target KOA proteins

The 3D structures of key target proteins a) TNF-α (PDB ID: 1TNF)[21], b) IL-1β (PDB ID: 2I1B)[22], and c) NLRP3 (PDB ID: 7ALV)[23] – were downloaded from the RCSB Protein Data Bank in the .pdb format (Figure 2). Structural preparation and optimization were conducted using the protein preparation suite, which involved the removal of water molecules, heteroatoms, and co-factors, retaining only the protein residues essential for further analysis. The purpose of protein optimization was to stabilize the structure of the macromolecule and shorten the time of macromolecular docking with ligands.[21]

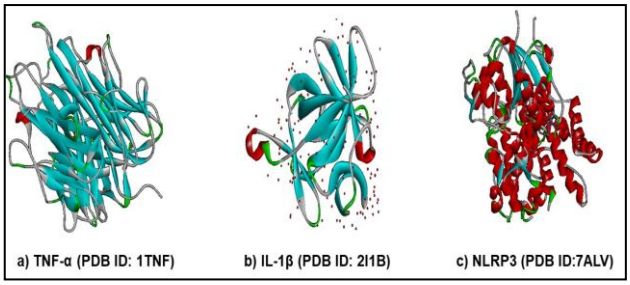

Figure 2: a) TNF-α (PDB ID: 1TNF); b) IL-1B (PDB ID: 2I1B); c) NLRP3 (PDB ID: 7ALV) molecular structure (taken through visualization with DS visualizer software).

Preparation of ligand

Based on the literature review for KOA, we identified 15 active compounds from Zingiber officinale, 3D structures were retrieved in (.sdf) format from the PubChem Database (Figure 3), and their molecular energies were minimized using the Energy minimization module in Biovia software.[24]

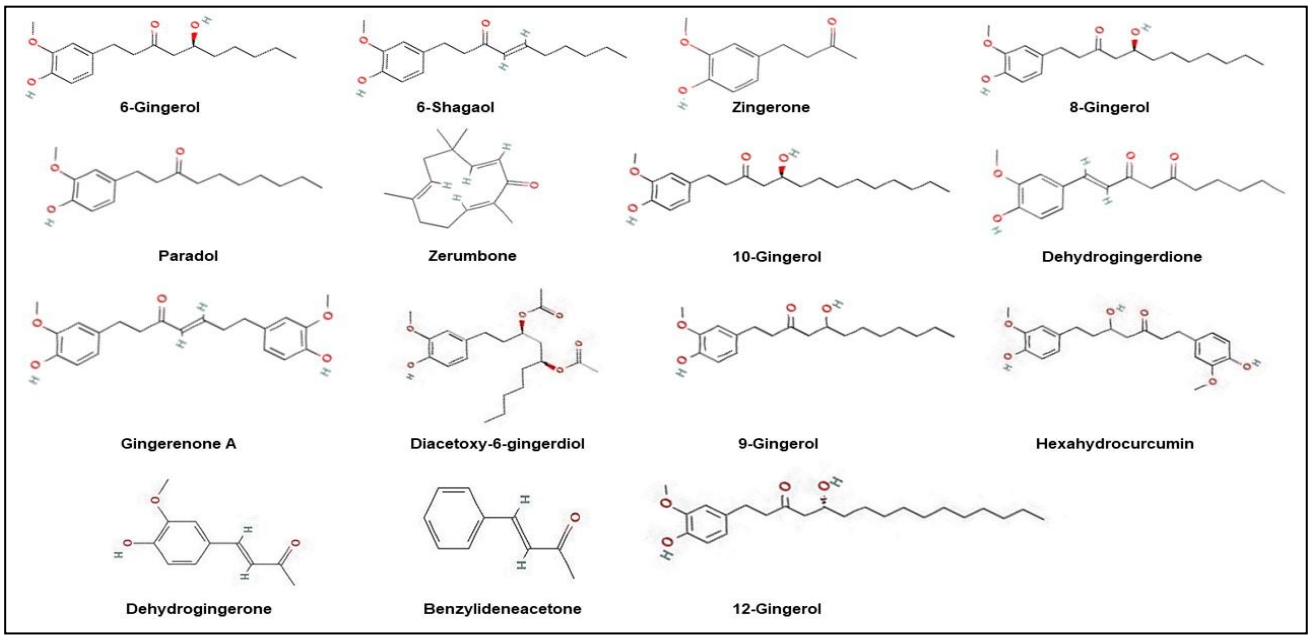

Figure 3: 2D Molecular structure of 15 ligands.

Insilco molecular docking

Before carrying out the molecular docking simulation, identifying the number of rotatable bonds to determine the flexibility of the used ligands were undertaken and stability of the rotatable bonds which were proportional were scored to the flexibility of the identified ligands. Data on the number of ligands and its characteristics has been listed (Table 1). The energy-minimized ligands (.sdf) and protein structures (.pdb) were converted into PDBQT format (.pdbqt) to facilitate molecular docking. Protein–ligand docking was carried out using the Glide docking module within the Schrödinger Suite. Prior to docking, the receptor grid was generated around the active site residues, as defined by co-crystallized ligands or literature-reported binding sites. The docking protocol employed the Standard Precision (SP) mode to predict binding affinities, with the scoring function evaluating key interactions such as hydrogen bonding, hydrophobic contacts, and electrostatic complementarity. Docking results were assessed based on Glide docking scores and the number of hydrogen bonds formed between the ligands and target proteins.[24]

Table 1: Characteristics of test-ligands.

No.	Compound name	Pubchem CID	LOGP	Molecular weight (g/mol)	Number of hydrogen bond acceptors	Number of hydrogen bond donors	Rotatable bond
1	6 -Gingerol	442793	2.5	294.4	4	2	10
2	6-Shogaol	11152	3.7	276.4	3	`1	9
3	Zingerone	31211	0.8	194.23	3	1	4
4	8-Gingerol	168114	4.2	322.4	4	2	12
5	Paradol	94378	3.8	278.4	3	1	10
6	Zerumbone	5470187	3.9	218.3	1	0	0
7	10-Gingerol	168115	5.3	350.5	4	2	14
8	Dehydrogingerdione	9796015	3.5	290.4	4	1	9
9	Gingerenone a	5281775	3.7	356.4	5	2	9
10	Diacetoxy-6-gingerdiol	57341725	4.8	380.5	6	1	14
11	9-Gingerol	24826452	4.7	336.5	4	2	13
12	Hexahydrocurcumin	5318039	2.7	374.4	6	3	10
13	Dehydrozingerone	53544238	1.7	192.2	3	1	3
14	Benzylideneacetone	637759	2.1	146.1	1	0	2
15	12- Gingerol	118547702	6.4	378.5	4	2	16

RESULTS

Molecular docking studies revealed that all synthesized ginger derivatives displayed strong binding affinities toward the respective receptor binding sites. The docking data were analyzed to determine optimal ligand-receptor interactions, emphasizing binding with low binding energy, and shortest favorable hydrogen bond distance. The docking models that were chosen had the most negative bond energy values indicating strong interactions. We used TNF-α, IL-1β, NLRP3 and studied against the 15 derivatives selected for KOA (Literature survey).

Docking of ligands - TNF-α receptor

The binding affinities and interaction profiles of the 15 ginger derivatives with TNF-α (PDB ID: 1TNF) were assessed via molecular docking simulations. Key binding parameters including hydrogen bond interactions, and docking energies were analyzed to determine the binding efficacy and stability of each ligand-receptor complex. 6-gingerol, Zingerone and Hexahydro curcumin formed strong interactions with GLN102 (1.96 Å), LYS98 (1.81 Å and 2.95 Å), GLY102 (1.97 Å and 3.05 Å) and stable binding conformation within the active site of TNF-α. The docking energies corresponding to these interactions ranged from 33.99 to 48.9 kcal/mol, with the most favorable interaction observed at 33.9 kcal/mol, indicating a highly stable and potentially bioactive ligand-receptor complex.

Zingerone, although structurally simpler, also formed hydrogen bonds with LYS98, with docking energies up to 33.99 kcal/mol. However, the binding distances were generally less favorable compared to those of 6-gingerol, reflecting comparatively weaker interactions and a lower predicted binding affinity. Hexahydro curcumin displayed moderate binding characteristics, forming interactions with GLN102 at comparable interatomic distances. Docking scores for hexahydro curcumin interactions were 48.90 kcal/mol, suggesting moderate binding strength within the TNF-α active site.

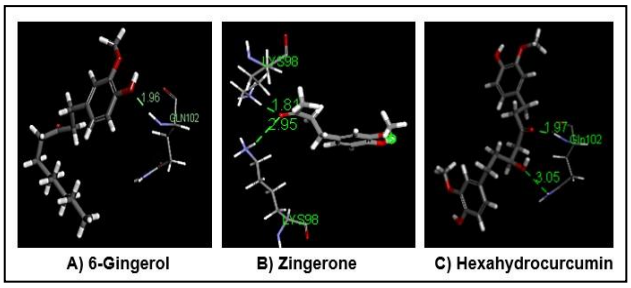

Figure 4: Molecular docking (A) 6-Gingerol; (B) Zingerone; (C) Hexahydrocurcumin ligands to TNF-α (3d visualization).

Hence, 6-gingerol was effective and showed the strongest and consistent interaction with TNF-α, marked by favorable binding energies and stable hydrogen bonds followed by zingerone. These findings support 6-gingerol as a potent anti-inflammatory agent targeting TNF-α and may warrant further investigation in combination or as structural analogs for therapeutic optimization (Figure 4) (Table 2).

Table 2: Molecular interactions with TNF-α.

Receptor name	Ligand	Receptor Interacting atoms	Ligand Interacting atoms	Distance	Docking energy
TNF-α	6-Gingerol	GLN102-NH	O	1.96	48.343
	6-Shagaol	LYS98-NH	O	2.65	34.4748
	Zingerone	LYS98-NH	O	1.81	33.9944
		LYS98-NH	O	2.95	
	8-Gingerol	GLY121-NH	O	2.54	-784.668
	Paradol	GLN102-NH	O	2.76	61.721
	Zerumbone	GLN102-NH	O	2.01	-30.2631
	10-Gingerol	GLN102-NH	O	2.78	46.0651
	Gingerone-a	GLN102-NH	O	2.37	39.2922
	9-Gingerol	GLN102-NH	O	2.55	47.1993
	Hexahydrocurcumin	GLN102-NH	O	1.97	48.9079
		GLN102-NH	O	3.05	
	Dehydrozingerone	LYS98-NH	O	2.65	34.4748
	12-Gingerol	GLN102-NH	O	2.45	48.3989

Docking of ligands - IL-1βreceptor

Molecular docking simulations were conducted to evaluate the binding affinity of ginger-derived bioactive compounds with the interleukin-1 beta (IL-1β) receptor (PDB ID: 2I1B). The docking scores, interaction residues, and bond distances are summarized in (Figure 5) (Table 3).

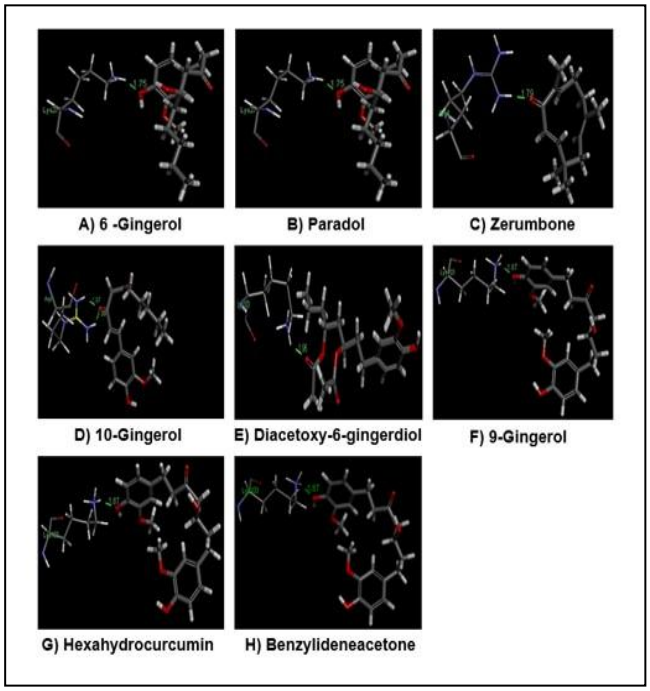

Figure 5: Molecular docking (A) 6 -Gingerol; (B) Paradol; (C) Zerumbone; (D) 10-Gingerol; (E) Diacetoxy-6-gingerdiol; (F) 9-Gingerol; (G) Hexahydrocurcumin; (H) Benzylideneacetone ligands to IL-1β (3D visualization).

Notably, 6-gingerol, one of the primary active constituents of ginger, showed a docking energy of 24.1806 kcal/mol and interacted with LYS27 via an oxygen atom at a distance of 1.75 Å indicating the strongest binding affinity with the IL-1β receptor. Several other compounds, including Paradol, Diacetoxy-6-gingerdiol, 9-gingerol, hexahydrocurcumin, and benzylideneacetone interacted primarily with LYS103, with docking energies ranging from 21.5502 to 33.3187 kcal/mol, forming hydrogen bonds within a range of 1.79 to 1.96 Å. Interestingly,12-gingerol uniquely interacted with THR147 (2.87 Å), while zerumbone displayed strong interaction with ARG4a at 1.79 Å and a docking energy of -38.0246 kcal/mol, suggesting selective receptor targeting.

These findings suggest that 6-gingerol forms the most promising ginger metabolites for IL-1β inhibition, while other compounds like Paradol and Zerumbone may also contribute to anti-inflammatory activity through moderate receptor interactions.

Docking of NLRP3 receptor (PDB ID: 7ALV)

To evaluate the potential anti-inflammatory activity of ginger-derived phytochemicals against the NLRP3 receptor (PDB ID: 7ALV), molecular docking analyses were performed. The binding affinities, interacting residues, bond distances, and docking energies have been summarized in (Figure 6) (Table 4).

All ligands demonstrated interactions primarily with the ARG578 residue of the receptor through hydrogen bonding with the NH group, indicating a conserved binding site preference. 8-gingerol, and 10-gingerol showed identical interaction patterns with ARG578-NH, forming dual hydrogen bonds at distances between 1.87–1.91 Å. These compounds exhibited docking energy of 41.3116 kcal/mol, indicating strong interaction and high stability of the ligand-receptor complex.

Table 3: Molecular interactions with IL-1β.

Receptor name	Ligand	Receptor interacting atoms	Ligand interacting atoms	Distance (AO)	Docking energy (kcal/mol)
Il-1β	6-Gingerol	LYS27	O	1.75	24.1806
	6-Shogaol	SER43	O	3.0	-891.548
		GLY61	O	2.90	
	Zingerone	LEU20	O	2.89	-274.392
	8-Gingerol	LYS103	O	2.24	19.4107
		ARG4	O	2.07	
	Paradol	LYS103	O	1.79	27.3454
	Zerumbone	ARG4A	O	1.79	-38.0246
	10-Gingerol	ARG4	O	1.97	14.3635
		ARG4	O	1.99	
	Dehydrogingerdione	CYS8	O	2.35	-786.296
	Gingerenone a	LYS103	O	2.31	11.5202
	Diacetoxy-6-gingerdiol	LYS103	O	1.96	33.3187
	9-Gingerol	LYS103	O	1.87	21.5571
	Hexahydrocurcumin	LYS103	O	1.87	21.5571
	Dehydrozingerone	LEU60	O	2.84	-283.741
	Benzylideneacetone	LYS103	O	1.87	21.5571
	12- Gingerol	THR147	O	2.87	27.3244

Table 4: Molecular interactions with NLRP3 (PDB ID: 7ALV).

Receptor name	Ligand	Receptor Interacting atoms	Ligand Interacting atoms	Distance	Docking energy
Nlrp3	6-Gingerol	ARG578-NH	O	2.15	41.995
		ARG578-NH	O	2.55	
	6-Shagaol	ARG578-NH	O	2.63	26.8152
		ARG578-NH	O	2.83	
	8-Gingerol	ARG578-NH	O	1.87	41.3116
		ARG578-NH	O	1.91	
	Paradol	ARG578-NH	O	2.25	49.825
	Zerumbone	ARG578-NH	O	2.06	-32.122
		ARG578-NH	O	2.19	
	10-Gingerol	ARG578-NH	O	1.87	41.3116
		ARG578-NH	O	1.91	
	Dehydrogingerdione	ARG578-NH	O	2.01	39.7574
		ARG578-NH	O	2.28	
	Gingerenone a	ARG578-NH	O	2.83	27.9554
	9-Gingerol	GLN624-NH	O	2.44	47.008
	Hexahydrocurcumin	GLN624-NH	O	2.09	39.0276
	Dehydrozingerone	VAL353-NH	O	2.91	21.6656
	Benzylideneacetone	LYS232-NH	O	1.76	25.1927
		GLY229-NH	O	2	
	12- Gingerol	ARG578-NH	O	2.63	45.4132
		GLN624-NH	O	2.37	

Benzylideneacetone and Dehydrozingerdione displayed unique interactions with LYS232-NH andARG578-NH, with corresponding docking scores of 25.1927 kcal/mol and 39.7574 kcal/mol, respectively. Other compounds, such as Hexahydro curcumin formed stable interactions primarily with GLN624-NH with docking scores of 39.0276 kcal/mol. Notably, paradol and 9-gingerol showed distinct interaction profiles. Paradol interacted with ARG578-NH (2.25 Å) and yielded the highest docking energy (49.825 kcal/mol), while 9-gingerol interacted with GLN624-NH (2.44 Å) with a docking energy of 47.008 kcal/mol.

Overall, the docking data suggest that 8-gingerol, and 10-gingerol may have the most potent inhibitory interaction with the NLRP3 receptor, while other ginger-derived compounds such as Benzylideneacetone, Dehydro-zingerone and Hexahydro curcumin showed weak binding potential. These findings reinstate the beneficial effects of ginger derivatives as promising natural inhibitor(s) targeting NLRP3 mediated inflammatory signaling in KOA (graphical abstract).

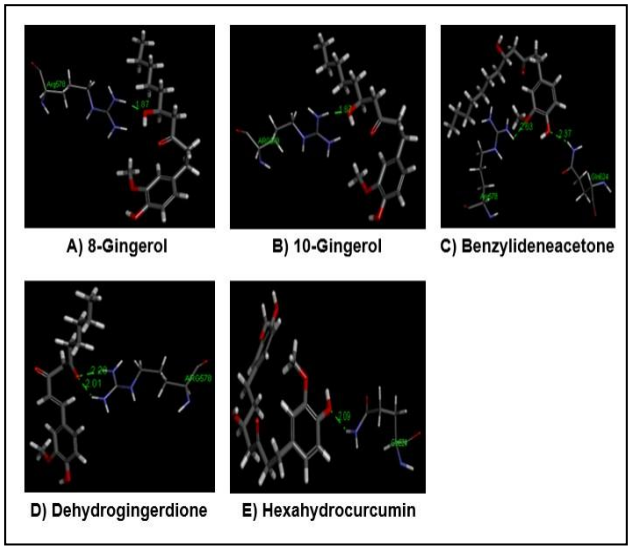

Figure 6: Molecular docking (A) 8-Gingerol; (B)10-Gingerol; (C) Benzylideneacetone; (D) Dehydrozingerdione; (E) Hexahydro curcumin ligands to NLRP3 (3D visualization).

DISCUSSION

Inflammation is viewed as an important pathophysiological event which exacerbates the disease progression(s) leading to the death of the organ or site.[25-27] Indeed, in similar lines, studies in obesity induced KOA presenting with chronic grade inflammation show increased expression of free radicals/orchestrated by quantitative increase in pro-inflammatory cytokines (TNF- α, IL-1β, IL-6, IL-18).[25-27] Also, appreciable alterations in cytoarchitecture of the knee joints affecting the functional responses of the target organ either due to apoptotic or necrotic death has been reported.[25] In fact, up-regulated expression of pro-inflammatory cytokines have shown to correlate underlining several inflammatory conditions such as multiple myeloma, rheumatoid arthritis, T1D and T2D, cancer etc suggesting for gravity of disease memory at the target organ.[25-27]

Ginger (Zingiber officinale Roscoe) and its bioactive derivatives have been extensively investigated for their anti-inflammatory and immunomodulatory properties. The present study explored for their synergistic and molecular interactions i.e. docking of key ginger-derived ligands with hall markers of inflammation underlining KOA including TNF-α, IL-1β, and the NLRP3 inflammasome. Molecular docking results captured in the present study demonstrate 6-gingerol as a potent and beneficial derivative based on its affinity of strong interaction with TNF-α and IL-1β receptors, which form hall markers of inflammatory targets in KOA implicated for cartilage degeneration (Graphical Abstract). Parallelly, reports by Tripathi et al have shown the protection /anti-inflammatory effects of 6-gingerol against TNF-α and by IL-1β tested in macrophage cell line.[28] Further, impetus obtained from our earlier data in an obesogenic milieu using 3T3 cell lines undoubtedly exemplify 6-gingerol for the anti-inflammatory role vis-a-vis with down regulated mRNA expression of TNF-α and IL-1β.[29] Also HBE-LBD (molecular Ligand interactions) for 6-gingerol show i.e GLN102-NH for TNF-α (1.96 Å/48.343kcal/mol) and for IL-1β / LYS27 (1.75 Å/24.18 kcal/mol) supporting its candidature to ameliorate inflammatory lesion in KOA. Zerumbone yet another derivative closer to 6-gingerol in the binding affinity can also be viewed as an important anti-inflammatory, evidenced by decreased expression of NLRP3, ASC and also of Caspase-1, IL-1β and TNF-α secretion showed in macrophage cell line system.[30] Studies have advocated therapeutic effects of 6-gingerol in lipopolysaccharide-stimulated mouse macrophages to suppress ROS generation and iNOS expression through inhibition of PKC-α and NF-κB pathways, to highlight the multi-targeted/ anti-inflammatory functions of ginger, used on a daily basis across the globe as culinary.[31]

Inflammasomes results for cellular and metabolic impairments (inflammation, mitochondrial dysfunction, ion imbalances) activating the cytosolic protein complex like PAMPs/DAMPs.[7,8,32] Our docking data on ginger derivatives like 8-gingerol and 10-gingerol demonstrated conserved interactions with ARG578-NH, forming dual hydrogen bonds with high docking energies (~-41.3 kcal/mol), suggests strong and specific binding at target site. During inflammation, inflammasome initiate caspase-1–mediated processing of IL-1β and IL-18 and activate innate immunity and inflammation by up regulating pyroptosis, an inflammatory form of cell death.[5-9] Studies show that dysregulation of inflammasomes particularly NLRP3,forms an important confounding factor to predispose to metabolic syndrome (Obesity T2D,CVDs ,hypertension, KOA etc.) interfacing to systemic inflammation.[8,31-34] Corroborating with other independent studies also demonstrated NLRP3 activation to neuroinflammatory diseases including Alzheimer's, Parkinson's, and multiple sclerosis which have been on the rise across the globe.[34] Paradol also showed high binding affinity (1.79 Aº) similar to 6-gingerol to elicit its potent antioxidant as well as an anti-inflammatory functions exemplified in ulcerative colitis model system vis-a-vis in macrophage cell lines to suppress the levels of NLRP3, ROS, TNF-α, IL-6 and IL-1β levels, and in preclinical models presenting with joint inflammation.[35] These findings go in hand with reported work particularly 10-gingerol and shogaols to significantly inhibit canonical NLRP3 inflammasome–mediated IL-1β secretion in LPS-primed, ATP-activated THP-1 macrophages.[36-37] In similar

lines other phytochemicals Like Zerumbone showed appreciable interactions with ARG4a of IL-1β yielding a docking energy of –38.0 kcal/mol and may elicit their effect to attenuate NF-κB signaling and activation of NLRP3 inflammasome shown in psoriasis models.[38,39] Although direct molecular docking data for 8-gingerol and 10-gingerol are not available, similar inhibitory patterns with 6-shogaol ≈ 8-shogaol > 10-gingerol > 8-gingerol, have been well documented to correlate with their inhibitory strengths on iNOS, IL-1β, and TNF-α expression.[40] In BV2 microglia cells Hexahydro curcumin-a reduced analog of curcumin-showed moderate cross-reactivity particularly through GLN624 (NLRP3) and GLN102 (TNF-α). Such multi-receptor binding potential suggests that hexahydro curcumin may be optimized for combination therapies or structural modifications. Collectively, these findings support that 8 and 10-gingerol modulate NLRP3 inflammasome activity via transcriptional priming blockade and caspase-1 inhibition as depicted in (Graphical Abstract).[8]

Our findings advocate for the multi-target binding capability of ginger phytochemicals and their potential as natural anti-inflammatory agents. Their consistent interaction with conserved residues such as LYS, GLN, and ARG across all receptor does indicate their functional roles for future structure-activity relationship (SAR) studies in disease management. Since KOA is presented with cartilage degeneration and dysfunction of joints, our molecular docking approach does throw light on the potential and beneficial effects of 6-gingerol, Zerumbone, Paradol ,8-gingerol, and 10-gingerol as anti-inflammatory due to their inhibitory effects regulating inflammation-mediated signaling pathways. It appears logical for us to suggest ginger /derivatives as a promising molecule for the treatment of KOA as it is a culinary product and contributes to wealth of nutrition. Fresh ginger contributes for 1.03–3.05 mg/g of 6-gingerol, 0.105–0.312 mg/g of 8-gingerol, and 0.078–0.425 mg/g of 10-gingerol.

CONCLUSION

The inherent features of ginger have been attributed to their multiple health spectral effects, well documented since ancient times vis a vis being non-toxic, easily absorbed and relatively low-cost dietary supplement(s) paves way as an important dietary component and need to explore. We advocate synergistic effects of 6-gingerol, Zerumbone, Paradol, 8-gingerol, and 10-gingerol either in combination or per se carried out in preclinical model of KOA, would pave way to understand the dynamics of interactions, ligand stability and which would delineate the mechanism(s) to ginger derivatives curb inflammation-driven degenerative diseases.

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REFERENCES

1. Gill TK, Mittinty MM, March LM, Steinmetz JD, Culbreth GT, Cross M, et al. Global, regional, and national burden of other musculoskeletal disorders, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatol. 2023;5(11):e670-82.
2. Lv Y, Sui L, Lv H, Zheng J, Feng H, Jing F. Burden of knee osteoarthritis in China and globally from 1992 to 2021, and projections to 2030: a systematic analysis from the Global Burden of Disease Study 2021. Front Public Health. 2025;13:1543180.
3. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The lancet. 2020;396(10258):1204-22.
4. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.
5. Scanzello CR. Role of low-grade inflammation in osteoarthritis. Curr Opin Rheumatol. 2017;29(1):79-85.
6. McAllister MJ, Chemaly M, Eakin AJ, Gibson DS, McGilligan VE. NLRP3 as a potentially novel biomarker for the management of osteoarthritis. Osteoarthritis Cartilage. 2018;26(5):612-9.
7. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol. 2019;19(8):477-89.
8. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An overview of mechanisms of activation and regulation. Int J Mol Sci. 2019;20(13):3328.
9. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7(1):33-42.
10. Raju SS, Niranjan T, Pandiyan P, Snehitha MS. A review of an early detection and quantification of osteoarthritis severity in knee using machine learning techniques. InIOP conference series: materials science and engineering. 2021;1057(1):012095.
11. Liu YR, Wang JQ, Li J. Role of NLRP3 in the pathogenesis and treatment of gout arthritis. Front Immunol. 2023;14:1137822.
12. Kitagawa T, Isaji Y, Sasaki D, Onishi K, Hayashi M, Okuyama W. Effectiveness of exercise therapy in patients with knee osteoarthritis: an overview of systematic reviews. BMJ open. 2025;15(7):e093163.

13. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet. 2012;379(9823):1331-40.
14. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti - inflammatory drugs. N Engl J Med. 1999;340(24):1888-99.
15. Semwal RB, Semwal DK, Combrinck S, Viljoen AM. Gingerols and shogaols: important nutraceutical principles from Zingiber officinale. Phytochemistry. 2015;117:554-68.
16. Frondoza CG, Sohrabi A, Polotsky A, Phan PV, Hungerford DS, Lindmark L. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cellular & Developmental Biology-Animal. 2004;40(3):95-101.
17. Ruangsuriya J, Budprom P, Viriyakhasem N, Kongdang P, Chokchaitaweesuk C, Sirikaew N, et al. Suppression of Cartilage Degradation by Zingerone Involving the p38 and JNK MAPK Signaling Pathway. Planta Med. 2017;83(4):268-76.
18. Shen CL, Smith BJ, Lo DF, Chyu MC, Dunn DM, Chen CH, et al. Dietary supplementation with ginger root attenuates knee osteoarthritis in a rat model: role of MMPs and cytokines. J Med Food. 2012;15(6):545-52.
19. Grzanna R, Lindmark L, Frondoza CG. Ginger-an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005;8(2):125-32.
20. Mozaffari-Khosravi H, Naderi Z, Dehghan A, Nadjarzadeh A, Fallah Huseini H. Effect of ginger supplementation on proinflammatory cytokines in patients with knee osteoarthritis: a randomized controlled trial. J Nutr Gerontol Geriatr. 2016;35(3):209-18.
21. Naismith JH, Devine TQ, Kohno T, Sprang SR. Structures of the extracellular domain of the type I tumor necrosis factor receptor. Structure. 1996;4(11):1251-62.
22. Priestle JP, Schär HP, Grütter MG. Crystallographic refinement of interleukin 1 beta at 2.0 A resolution. Proc Natl Acad Sci. 1989;86(24):9667-71.
23. Dekker C, Mattes H, Wright M, Boettcher A, Hinniger A, Hughes N, et al. Crystal structure of NLRP3 NACHT domain with an inhibitor defines mechanism of inflammasome inhibition. J Mol Biol. 2021;433(24):167309.
24. Kundur S, Perugu S. Quantification of total phenols in Coleus forskohlii and inhibition of aldose reductase by rosmarinic acid. Journal of Molecular Structure. 2024;1312:138435.
25. Kotikalapudi N, Sampath SJ, Sukesh Narayan S, Ramesh R B, Nemani H, Mungamuri SK, et al. The promise (s) of Mesenchymal stem cell therapy in averting preclinical diabetes: lessons from in vivo and in vitro model systems. Sci rep. 2021;11(1): 16983.
26. Sampath SJP, Rath SN, Kotikalapudi N, Vijayalakshmi V. Beneficial effects of secretome derived from mesenchymal stem cells with stigmasterol to negate IL-1β-induced inflammation in-vitro using rat chondrocytes—OA management. Inflammopharmacology. 2021;29(6):1701-17.
27. Nanchari SR, Perugu S, Venkatesan V. Molecular docking studies to understand the potential role of ginger compounds (6-gingeroland 6-shogaol) on anti-angiogenic and anti-lymphangiogenic mechanisms. International Journal of Chemistry. 2020;12(1):61-8.
28. Tripathi S, Maier KG, Bruch D, Kittur DS. Effect of 6-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. J Surg Res. 2007 ;138(2):209-13.
29. Sampath SJ, Birineni S, Perugu S, Kotikalapudi N, Venkatesan V. Therapeutic efficacy of 6-gingerol and 6-shogaol in promoting browning of white adipocytes vis-à-vis enhanced thermogenesis portrayed in high fat milieu. Food Bioscience. 2021;42:101211.
30. Su CC, Wang SC, Chen IC, Chiu FY, Liu PL, Huang CH, et al. Zerumbone suppresses the LPS-induced inflammatory response and represses activation of the NLRP3 inflammasome in macrophages. Frontiers in Pharmacology. 2021 May 11;12:652860.
31. Lee TY, Lee KC, Chen SY, Chang HH. 6-Gingerol inhibits ROS and iNOS through the suppression of PKC-α and NF-κB pathways in lipopolysaccharide-stimulated mouse macrophages. Biochem Biophys Res Commun. 2009;382(1):134-9.
32. Robbins GR, Wen H, Ting JP. Inflammasomes and metabolic disorders: old genes in modern diseases. Molecular cell. 2014;54(2):297-308.
33. Han JH. Immuno-metabolic diseases and therapeutics: molecular mechanisms via inflammasome signaling. Cell Communication and Signaling. 2025;23(1):373.
34. Xu W, Huang Y, Zhou R. NLRP3 inflammasome in neuroinflammation and central nervous system diseases. Cell Mol Immunol. 2025;22:341-55.
35. Rafeeq M, Murad HAS, Abdallah HM, El-Halawany AM. Protective effect of 6-paradol in acetic acid-induced ulcerative colitis in rats. BMC Complement Med Ther. 2021;21(1):28.
36. Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, et al. Bioactive compounds and bioactivities of ginger (Zingiber officinale Roscoe). Foods. 2019;8(6):185.
37. Ho SC, Chang YH. Comparison of inhibitory capacities of 6-, 8- and 10-gingerols/shogaols on the canonical NLRP3 inflammasome-mediated IL-1β secretion. Molecules. 2018;23(2):466.
38. Su CC, Wang SC, Chen IC, Chiu FY, Liu PL, Huang CH, et al. Zerumbone suppresses the LPS-induced inflammatory response and represses activation of the NLRP3 inflammasome in macrophages. Frontiers Pharmacol. 2021;12:652860.

39. Lin J, Fang Y, Cao Y, Ma L, Tao M, Wang X, et al. Zerumbone attenuates the excessive proliferation of keratinocytes in psoriasis mice through regulating NLRP3/NF-κB pathway. Toxicol Res. 2023 ;12(4):658-64.
40. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol. J Ethnopharmacol. 2010;127(2):515-20.

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