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Assessment of Antimicrobial, Antioxidant, Anti-inflammatory, and Anticancer Properties of Polyphenols in Ragi Plant

Vikil Ramesh, Megha Mathur, S. Kiran, N. Rajeswari and Shashank A. Tidke*

Dayananda Sagar college of Engineering (Visvesvaraya Technological University), Kumarswamy layout, Bangalore-560078, India

ABSTRACT

Background and Objectives: (*Eleusine coracana*) is a rich source of proteins, phytochemicals, and fibers with several health benefits. Cancer accounts for 12^{c}/o of death worldwide, which requires superior therapeutic strategies. Polyphenols are a class of phytochemicals in plant derived compounds, that has been reported to exhibit anticancer, antioxidant, anti-inflammatory and antimicrobial properties. The objective was to investigate the binding potential of selected polyphenols against probable drug targets of various types of cancer and provide an insight on the anti-inflammatory, antioxidant, and antimicrobial properties by using molecular docking method.

Materials and Methods: Ten receptors were analyzed for anticancer, two receptors for anti- inflammatory, three receptors for antioxidant, and five receptors for antimicrobial studies. The binding competences of polyphenol towards selected targets were studied by molecular docking.

Results: Affinity of polyphenols as an anticancer agent with respect specific targets viz CDKN1A, FOXO1, FGFR2, CTNNB1, and GST-PI was evident. The binding energies of docked complexes were found to be -116.56, -114.5, -110.38, -106.9, and -105.07 kcal/mol, respectively. In case of anti-inflammatory the best binding was seen in between COX-2 receptor with and COX-1 receptors. Antioxidant studies it was observed that SOD2 showed the best binding energy followed by SOD3. Followed by antimicrobial studies the best binding interaction some how were shown by IARS and PBP1a receptors.

Conclusion: Present studies revealed that polyphenols has superior interacting properties towards these cancer targets than their normal ligands and shows a strong approach to anti-inflammatory, antioxidant, and antimicrobial activity.

***Corresponding author**

Shashank A. Tidke, Dayananda Sagar college of Engineering (Visvesvaraya Technological University), Kumarswamy layout, Bangalore- 560078, India, Tel: +919880410079; E-Mail: shashank.tidke08@gmail.com

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Introduction

Ragi (*Eleusinecoracana*) is well known for its higher levels of dietary fibers, carbohydrates, and health beneficial phytochemicals. Which mainly helps in decreasing the level of diabetes and obesity in the human health [1]. Epidemiological studies had stated that consumption in whole grains cereals and their products can protect and reduce the risk of cardiovascular diseases, type 2 diabetes, and a wide range of other disorders [2]. Fortification process was carried with diets and for material which are rich source of phenolic acid (like; Ragi) has shown the properties like antimutagenic, antiglycemic, and antioxidant [3]. Nutritional potential of finger millet in terms of protein and carbohydrates are comparable higher than rice, wheat, and barley. Finger millet contains 5-8% proteins, 1-2% ether, 65-75% carbohydrates, 15-20% dietary fibers, (0.48%) phytates, polyphenols, tannins, and (0.61%) trypsin inhibitor factor (shows anticancer activity) [4]. Polyphenols are a large and diverse class of compounds, which are naturally present in food plants. Phenolic (hydroxybenzene) are ubiquitous in plant foods consumed by humans and animals [5]. Polyphenols like flavonoids, tannins, and phenolic acid are present in small quantities [6]. These compounds have properties like anticancer, antioxidant, anti-inflammatory, and antimicrobial activities [7]. Compounds like Epigallocatechin, and FeruloylArabinoxylans shows the properties of anti-inflammatory, anticancer, and antioxidant activities respectively. Furthermore, we analyzed anticancer, anti-inflammatory, antioxidant, and antimicrobial receptors against these compounds. Multi receptor docking has been performed for predictive assessment and evaluation of mode of action of these compounds (polyphenols).

Materials and Methods

Location: Work has been done in Bioinformatics Lab of Biotechnology Department, Dayananda Sagar College of Engineering Bangalore.

Selection of receptors: Various receptors were chosen for this study based on their functional role and pathways.

According to the reported target sites of ligands the receptors were chosen for current studies listed in (Table 1). The three-dimensional structures of these receptors were retrieved from PDB (Protein Database) [8]. The pathways of these receptors were analysed using KEGG (Kyoto Encyclopaedia of genes

and genome) pathways [9]. Various pathways were analysed which includes cervical tumor, gastric disease, colorectal tumor, endometrial tumor, thyroid tumor, oral disease, esophageal tumor, choriocarcinoma, glioma, chalangiocarcinom, prostate growth, dangerous pleural mesothelioma, synovial sarcoma, Hodgkin lymphoma, and longevity regulating pathways. Two receptors COX-1 and COX-2 have been reported for anti-inflammatory activities [10]. There receptors SOD2, SOD3, and CAT (catalase) have been reported for antioxidant activities [11]. Similarly, receptors for antimicrobial activity viz IARS, DHPS, Dd1, DHFR, and PBP1a were considered [12].

Table 1: Selection of probable drug targets from various types of cancers for structure based drug screening

Gene Name	Receptor Name	PDB id
Selected from cancer pathways from KEGG		
CDKN1A	Proliferating cell nuclear antigen	1AXC
CTNNB1	Beta-catenin	1JDH
EGF	Epidermal growth factor	1NQL
IGFI	Insulin-like growth factor 1	1TGR
GST-PI	Glutathione S-transferase Pi gene	2A2R
AKT2	Protein kinase B	2X39
FGFR2	Fibroblast growth factor receptor 2	3B2T
FOXO1	Fork head box protein o1	3CO6
EGFR	Epidermal growth factor receipts kinase	3P0Z
ERBB2	Human epidermal growth factor 2	3PP0
Anti-inflammatory receptors		
COX-1	Cytochrome C oxidase 1	1Q4G
COX-2	Cytochrome C oxidase 2	5F19
Anti-oxidant receptors		
CAT	Catalase	1DGF
SOD3	Extra cellular superoxide dismutase	2JLP
SOD2	Manganese-dependant superoxide dismutase	2P4K
Anti-microbial receptors		
IARS	Isoleucyl-tRNAsynthetase	1JZQ
DHPS	Dihydropteroatesynthetase	2VEG
Dd1	D alanyl-D-alanine synthetase	2ZDQ
DHFR	Dihydrofolate reductase	3SRW
PBP1a	Penicillin binding protein 1a	3UDI

Source: PDB (Protein Database)

Selection of Ligands

Structures of polyphenols (Epigallocatechin, and Feruloyl Arabinoxylans) were obtained from Chemspider database and PDB (Protein Database) [13]. The Pharmacokinetics properties of respective ligands were screened using pKCSM (Prediction of small-molecule Pharmacokinetics and toxicity) tool. The Pharmacokinetics profile of any compound defines it's absorption, distribution, metabolism, and excretion properties [14]. Many tools are available online for predicting the pharmacokinetics and toxicity properties of a compound using it's chemical structure or smiles, ranging from data-based approaches such as QSAR (Quantitative Structure-activity relationship), similarity searching [18],[19] and 3-dimensional QSAR [15-20].

Multi-Receptor Docking

Multi-receptor docking was performed to predict the anticancer, anti-inflammatory, antioxidant, and antimicrobial properties of the selected polyphenols (Epigallocatechin, and FeruloylArabinoxylans). Docking studies were performed by iGEMDOCK software [21]. The properties of active sites like physical and chemical properties will allow the recognition and binding of the ligand. Different conformations of docked structures were generated using the parameters (population size 200, generations 70, and solutions 10) and out of these, best confirmation were selected in terms of lowest binding energy.

Results and Discussions

Prediction of in Silico Anti-Cancer Properties of Feruloylarabinoxylan and Epigallocatechin

Multi-receptor docking was conducted to peruse the inhibitory activity of the ligands feruloylarabinoxylan and epigallocatechin with different cancer receptors that are contemplated as plausible drug targets. On the basis of the lowest binding energy, interactive residues and number of hydrogen bond, the best docked pose of structure was selected. Feruloylarabinoxylan was seen to have the best docked poses and the highest interactive energy amongst the polyphenols. Five vital receptors that showed the best binding associations are CDN1A, FOXO1, FGFR2, CTNNB1, and GST-PI. The docked energies of receptor-ligand complex-1 were found to be -116.56, -114.5, -110.38, -106.9, and -105.07 kcal mol^{-1}, respectively (Fig 1). Proliferating cell nuclear antigen(CDKN1A) is the driving force of several different cellular-level activity for example DNA replication, DNA repair, the over expression of this protein tends to cause prostate cancer [22,23]. The role of fork-head box protein o1 (FOXO1) in carcinogenesis was found to be basically in prostate cancer and pediatric malignant rhabdomyosarcomas [24]. Fibroblast growth factor receptor 2(FGFR2) was found to be present in breast cancer and lung cancer [25]. Over-expression of beta-catenin is seen in melanoma and leukaemia [26]. The expression of the protein Glutathione S-transferase pi gene(GST-PI) is specifically seen in gastric carcinoma [27]. The crucial interacting residues of CDN1A are LYS-13, ASN-84, ARG-146, and ARG-149. The interacting residues of FOXO1 are ARG-180, LEU-217, HIS-220, and ASN-240. For FGFR2 the important residues are PHE-492, GLN-494, ASN-549, ILE-563, and ASP-525. The interacting residues of CTNNB1 are SER-318, GLY-319, and ASN-326. For GST-PI the residues are SER-65, ARG- 70, and ASP-94 (Fig 2). Therefore from this study it is apparent that polyphenols have vast orbit ofinhibitory activities averse to the diverse cancer receptors . The prevailing inhibitory activity and supreme pharmacokinetic facets leading to polyphenols being the ideal therapeutic drug for a variety of cancer.

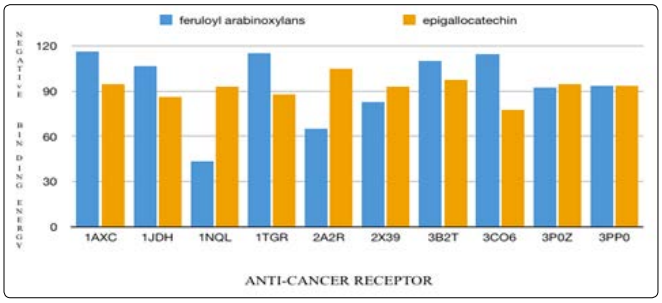

Figure 1: Molecular docking studies of polyphenols with cancer drug targets showing negative binding energy

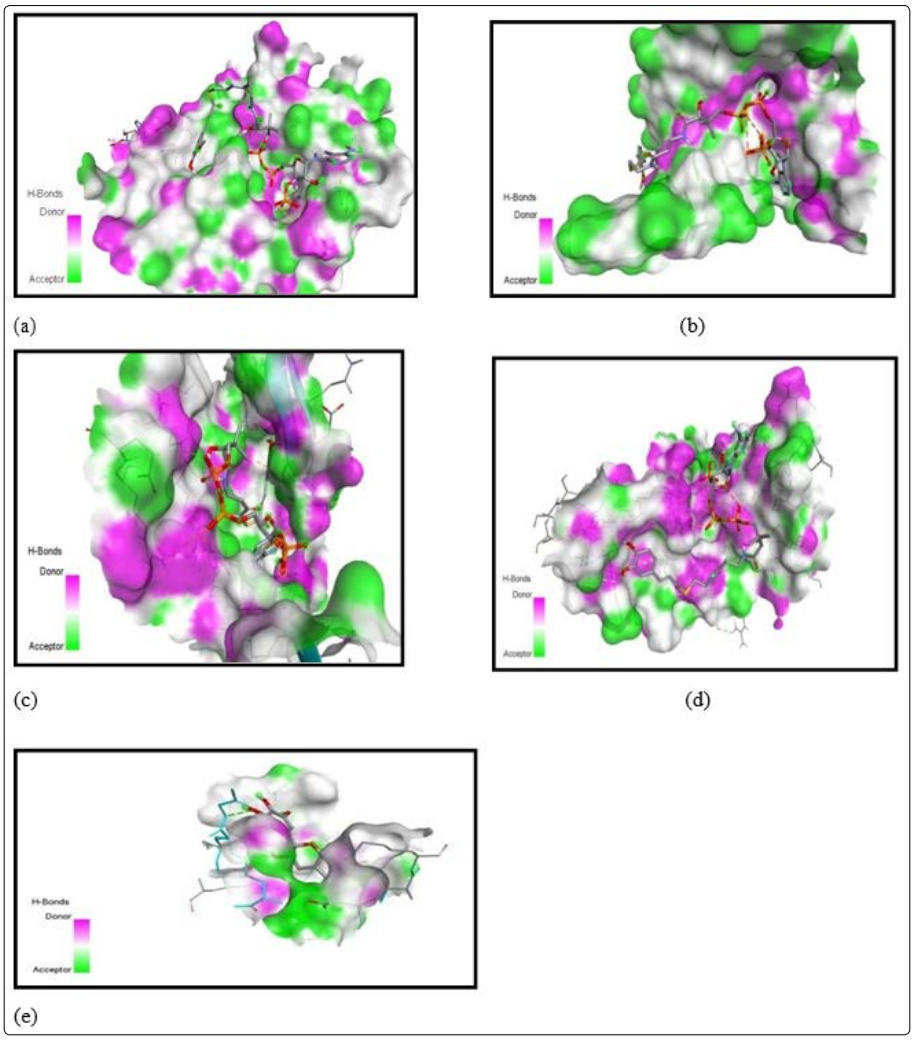

Figure 2 (a-e): Binding interaction of specific receptor target with feruloylarabonoxylan and epigallocatechin, (a) proliferating call nuclear antigen (CDNK1A), (b) Fork head box protein 01 (FOXO1), (c) Fibroblast growth factor receptor 2 (FGFR2), (d) Beta-catenin (CTNNB1) and (e) Glutathione S-transferase Pi gene (GST-PI)

Prediction of in Silico Anti-Inflammatory Properties of Feruloylarabinoxylan and Epigallocatechin

The docking studies of COX-1 and COX-2 proteins were done surmising the attributes of the polyphenols. Evidently polyphenols showed high interaction with the receptors. Epicallocatechin in particular was seen to have the highest interaction amongst the polyphenols. The best binding associations were of COX-2 receptor with epicallocatechin and COX-1 receptor with feruloylarabinoxylan. The respective docking energies of these complex were -115.45 and -97.23 kcal /mol (Fig 3). COX signalling is expressed in repercussion injury [28]. COX-1 and COX-2 proteins are seen to be expressed in carcinogenic pathways [29]. COX-1 and COX-2 proteins are are found in tissues, the former being found in normal tissue whereas the later being found in inflamed tissues [30]. The interacting residues of COX-1 with feruloylarabinoxylan are THR-111, ARG-114, SER-121, and BOG-754 and similarly the residues for COX-2 with epigallocatechin are HIS-30, GLN-42, ASN-43, ARG-44, CYS-47, GLN-451, and LYS-468 (Fig 4). It was therefore evident that polyphenols show supreme inhibitory properties against inflammatory disorder.

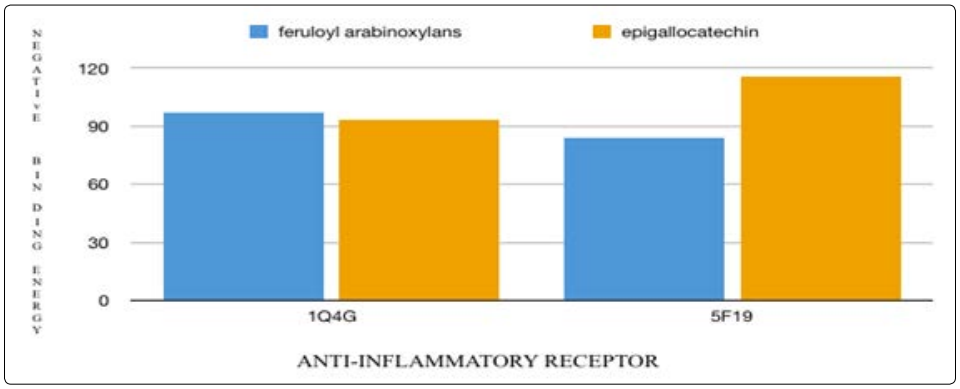

Figure 3: Molecular docking studies of polyphenols with anti-inflammatory targets showing negative binding energy

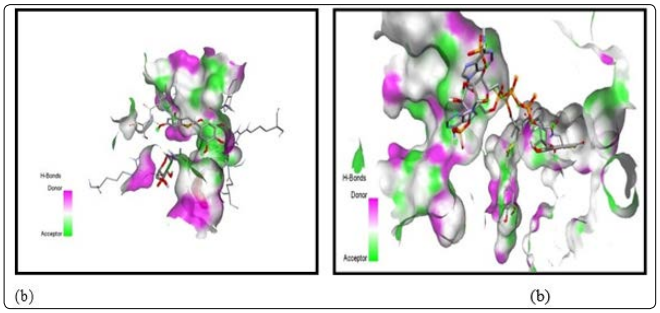

Figure 4(a-b): Binding interaction of specific receptor target with Epigallocatechin and feruloylarabinoxylan (a)Cytochrome C oxidase 2 (COX-2), and (b) Cytochrome C oxidase 1 (COX-1)

Prediction of in Silico Anti-Oxidant Properties of Feruloylarabinoxylan and Epigallocatechin

two main antioxidants receptors catalase, SOD2(manganese-dependant superoxide dismutase), and SOD3(extra cellular superoxide dismutase) were volunteered for the docking studies with the polyphenols feruloylarabinoxylan and epigallocatechin. Polyphenols are known to have antioxidant properties by its effect on plasma, transcription factor and enzymes [31]. Catalase plays an important part as an antioxidant enzyme [32]. Faulty functioning of catalase is capable of causes various diseases like diabetes mellitus, cardiovascular diseases, and bipolar disorder [33-35]. It also regulates the hydrogen peroxide [36]. SOD2 is that enzyme that converts superoxide to a mildly reactive hydrogen peroxide and it can plausibly cause neurodegenerative disorders like Alzheimer's and Parkinson [37]. SOD3 is an antioxidant enzyme present in the lungs [38,39]. This protein increases the vulnerability to chronic obstructive pulmonary lung diseases [40]. From the studies it was observed that SOD2 showed the best binding energy. The docking energies of the complexes were found to be -123.05, and -103.87 kcal mol $^{-1}$ respectively (Fig 5). The interacting residues of SOD2 with feruloylarabinoxylan are ARG-132, HIS-134, LYS-98, LYS 110, ARG-132, GLY- 133, and HIS-134. The residues for SOD3 with epigallocatechin are GLN-48, ARG-59, PRO-49, SER-50, and ARG- 59 (Fig 6). Therefore it is evident that SOD2 was the best antioxidant drug target followed by SOD3.

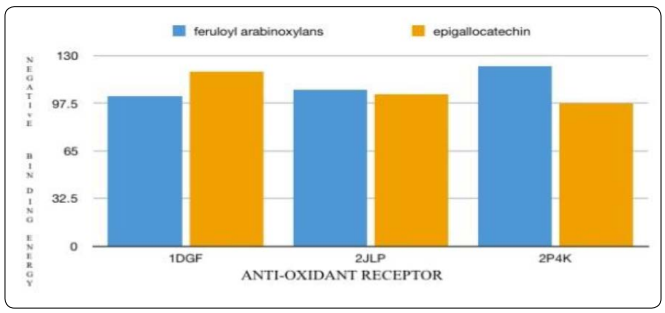

Figure 5: Molecular docking studies of polyphenols with anti-oxidant targets showing negative binding energy

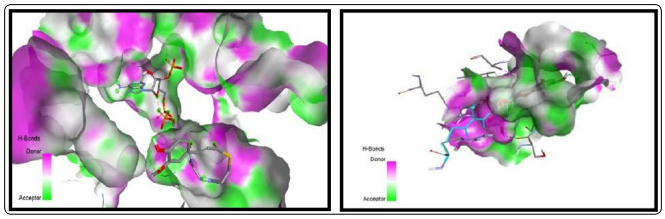

Figure 6(a-b): Binding interaction of specific receptor target with feruloyl arabinoxylan and epigallocatechin, (a) Manganese dependant superoxide dismutase (SOD2), and (b) Extra cellular superoxide dismutase (SOD3)

Prediction of in Silico Anti-Microbial Properties of Feruloylarabinoxylan and Epigallocatechin

Polyphenols surprisingly shows anti-microbial properties. For the *in silico* studies we used five important receptors namely IARS(isoleucyl-tRNAsynthetase), DHPS(dihydropteroate synthetase), Dd1(D alanyl-D-alanine synthetase), DHFR(Dihydrofolate reductase), and PBP1a(penicillin binding protein 1a). The best binding interaction some how were shown by IARS and PBP1a with former being docked with epigallocatechin and the later being docked with -1 feruloyl arabinoxylan with their respective docking energies being -150.82 and -117.84 kcal mol^{-1} (Fig 7). IARS is a protein that primarily helps in the growth of bacteria [41]. It basically decrypts the isoleucine codons [42]. Pencilin binding proteins in general helps in the biosynthesis of peptidoglycan and PBP1a the subunit is important in the development of resistance from penicillin [43]. The essential interacting residues of IARS with epigallocatechin are TRP-21, LYS-22, LYS-25, ILE-26, PHE-27, GLU-135, ILE-137, TYR-139, and VAL-141 and the residues for PBP1awith feruloylarabinoxylan are GLN-431, GLY-433, SER-434, ASN-489, ASN-674, ASP-675, and GLY-709 respectively (Fig 8).. Hence IARS is plausibly the best anti-microbial drug target receptor.

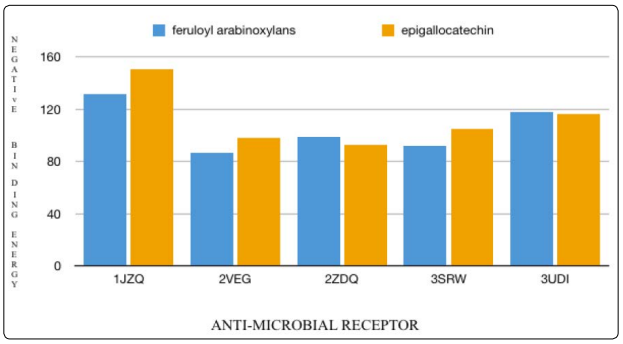

Figure 7: Molecular docking studies of polyphenols with anti-microbial targets showing negative binding energy

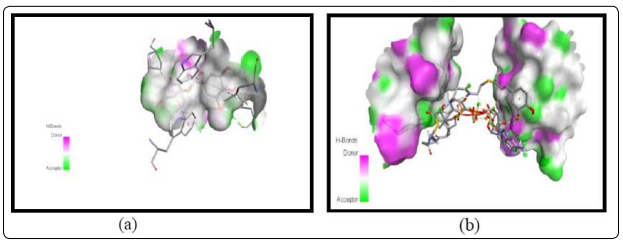

Figure 8(a-b): Binding interaction of specific receptor target with epigallocatechin and feruloyl arabinoxylan , (a) Isoleucyl- tRNA-synthetase (IARS), and (b) Penicllin binding protein 1a (PBP1a)

Conclusion

Polyphenols is a chief component of Poaceae family which exhibit antioxidant, anti-inflammatory, anti-microbial and anti-carcinogenic activities. Present study revealed that the inhibitory properties of polyphenols against various cancer drug targets by computer aided virtual screening. This comparative study revealed that polyphenols showed better inhibitory activities against the virulent gene products of Proliferating cell nuclear antigen (CDKN1A), Fork head box protein o1 (FOXO1), Fibroblast growth factor receptor 2 (FGFR2), Beta-catenin (CTNNB1), and Glutathione S- transferase Pi gene (GST-PI) than their native ligands. COX-1 protein was successfully docked onto Epigallocatechin, and FeruloylArabinoxylans for drug interaction studies with best binding energy showing the significance of COX 1 as anti-inflammatory target by Polyphenols. Polyphenols showed

best binding against SOD2 (Manganese-dependent superoxide dismutase) followed by SOD3 receptors. As similarly polyphenols showed best binding against IARS (Isoleucyl-tRNAsynthetase) antimicrobial receptor. Present data cover crucial landmarks for further studies to validate polyphenols as promising drug candidate against various cancers.

Significant Statement

The current study provide the complete knowledge on the binding potential of selected polyphenols such as Epigallocatechin, and FeruloylArabinoxylans towards the probable drug targets of various types of cancers and predict useful approaches on anti-inflammatory, antioxidant, and antimicrobial activities by computational modeling . To the best of our knowledge this is the one of the studies providing therapeutic potential of polyphenols towards priorities targets of cancers and highlighting their role as anti-inflammatory, antioxidant and antimicrobial agents. The present study provides novel insights for the selection and screening of these lead molecules as future therapeutics agents towards various types of cancers.

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