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Research Article
Assessment of Anticancer, Anti-inflammatory and Antioxidant Properties of Isoflavones Present in Soybean

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Abstract

Background and Objective: Soybean (*Glycine max*) is highly valued source of protein and vegetable oil with several health benefits such as low plasma cholesterol and preventing cancer. Cancer accounts for 10% of total death worldwide, which requires superior therapeutic strategies. Isoflavones are a class of plant-derived compounds, which is mainly produced by Fabaceae family that has been reported to exhibit anticarcinogenic, antioxidant and anti-inflammatory properties. The objectives was to investigate the binding potential of selected isoflavones against the probable drug targets of various types of cancer and provide an insight on the anti-inflammatory and antioxidant properties by computer assisted virtual screening method. **Materials and Methods:** Twenty two receptors were analyzed for anticancer, two for anti-inflammatory and three for antioxidant studies. The binding competences of isoflavones (Daidzein, Genistein and Glycitein) towards selected targets were studied by molecular docking. **Result:** Affinity of isoflavones as an anticancer agent with respect specific target viz EGF, NFKBIA, PIK3CA, PTEN and RB1 was evident. The binding energies of docked complex were found to be -103.59, -90.675, -100.73, -105.68 and -109.2 kcal mol^{-1}, respectively. COX-1 receptor showed best binding interaction with binding energies -110.38, -116.48 and -104.35 kcal mol^{-1}, respectively, Catalase receptor showed high-energy interaction with binding energies -100.66, -94.02 and -97.53 kcal mol^{-1}, respectively. Hence COX-1 and catalase were formed to be efficient target for anti-inflammatory and antioxidant site, respectively. **Conclusion:** Present study revealed that isoflavones has superior interacting properties towards these cancer targets than their normal ligands or predictable antitumor agents and strong approach to anti-inflammatory and antioxidant activity.

Key words: *Glycine max*, isoflavones, anticancer, anti-inflammatory, antioxidant, *In silico*

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Soybean [*Glycine max* (L.) Merrill] is known as the "Golden Bean" of the 20th century[1]. Soybean based foods have been reported to offer several health benefits such as lower plasma cholesterol[2], prevent cancer[3], improve bone mineral density[4] and provide protection against bowel and kidney disease[5]. These health benefits are caused by the presence of isoflavone, saponin, protein and peptide in soybean[5-7]. Isoflavones are a class of flavonoids, which are shown to have estrogenic activity in mammals[8]. Isoflavones also show antioxidant, anticancer, antimicrobial and anti-inflammatory properties[9]. Dower *et al.*[10] and Grace *et al.*[11] have demonstrated that the polyphenolic compounds of plant sources, in particular flavonoids, show anti-inflammatory activity both *in vitro* and *in vivo* models. Some epidemiological studies connected with high dose consumptions of soy isoflavones with multiple beneficial effects on prostate and breast cancers, osteoporosis atherosclerosis, menopausal symptoms, stroke and neurodegeneration have been reported[12,13]. Nagata[14] reported that the amount of soy isoflavones consumed, the form, food source, timing of isoflavone exposure, estrogen receptor and hormonal profile of individuals may modify the risk of breast cancer. In the present study we carried out *in silico* analysis interaction of isoflavones with receptors of different types of cancer included, gastric cancer, prostate cancer, malignant pleural mesothelioma, glioma, small cell lung cancer, endometrial cancer, breast cancer etc. Furthermore we analyzed anti-inflammatory and antioxidant receptors against isoflavones. Multi receptor docking has been performed for predictive assessment and evaluation of mode of action of isoflavones.

MATERIALS AND METHODS

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

Duration: The duration was from 15 November, 2017 to 10 January, 2018.

Selection of receptors: Receptors for the study were chosen based on functional role in cancer pathway. Based on the reported target site, the receptors chosen for current studies have been listed in Table 1. The three-dimensional structures of these receptors were retrieved from protein data bank (PDB) database[15]. The pathways were analyzed using Kyoto encyclopedia of genes and genomes database[16]. Various pathways were analyzed which includes cervical tumor, gastric disease, colorectal tumor, endometrial tumor, thyroid tumor, hepatocellular carcinoma, oral disease, esophageal tumor, bladder growth, choriocarcinoma, glioma, laryngeal disease, ovarian tumor, bosom growth, cholangiocarcinoma, alveolar rhabdomyosarcoma, prostate growth, dangerous pleural mesothelioma, synovial sarcoma, Hodgkin lymphoma, little cell lung malignancy, vulvar malignancy and longevity regulating pathways. Two receptors COX-1 and COX-2 have been reported for anti-inflammatory activities[17]. Similarly, receptors for antioxidant activity viz SOD-2, SOD-3 and catalase were considered[18].

Selection of ligands: Structures of isoflavones (Daidzein, Glycitein and Genistein) were obtained from ChemSpider Database[19]. The pharmacokinetics properties were screened using PRE-ADMET (incorporates absorption, distribution, metabolism and excretion) tool[20]. Drug-likeliness, ADMET profile were predicted for all the three ligands. PRE-ADMET incorporates pharmacokinetic parameters such as $CaCO_2$-cell (human epithelial colorectal adenocarcinoma cell lines) and MDCK (Madin-Darby Canine Kidney) cell models for oral medication assimilation forecast and skin porousness and human intestinal ingestion, demonstrated for oral and trans-dermal drug absorption prediction. Pre-ADMET predicts toxicity from Ames parameters and rodent carcinogenicity tests of rat and mouse[21]. Hence, pre-ADMET tool was used to predict pharmacokinetic of selected ligands (Table 2) for druglikness feature of isoflavones.

Multi-receptor docking: Multi receptor docking was performed to predict the anti-cancer, anti-inflammatory and anti-oxidant properties of the isoflavones. Docking studies were performed by iGemDock[22]. The structural and chemical properties of the active sites allow the recognition and binding of the ligand. Different bioactive conformations were generated with these parameters (population size 200, generations 70, solutions 10) and the best conformations were screened in terms of lowest binding energy generated in the clustering histogram.

RESULTS AND DISCUSSION

Predicted pharmacokinetic properties of soybean isoflavones: The ligands were predicted for pharmacokinetic properties using PRE-ADMET device. Drug resemblance, ADME

Table 1: Selection of probable drug targets from various types of cancers for structure based drug screening. The drug targets were screened based on the functionality role in the metabolic pathways of each type of cancer. The structural coordinates of these drug targets were retrieved from PDB

Gene name	Receptor name	PDB ID
Receptors selected from cancer pathways from KEGG		
CDKN1A	Proliferating cell nuclear antigen	1AXC
CTNNB1	Beta-catenin	1JDH
EGF	Epidermal growth factor	1NQL
EGFR	Epidermal growth factor receptor kinase	3POZ
ERBB2	Human epidermal growth factor 2	3PP0
AKT2	Protein kinase B	2X39
FGFR2	Fibroblast growth factor receptor 2	3B2T
FOXO1	Fork head box protein O1	3CO6
GST-PI	Glutathione S-transferase Pi gene	2A2R
IGF1	Insulin-like growth factor 1	1TGR
IGF1R	Insulin-like growth factor 1 receptor	1P4O
AR	Androgen receptor	2AX6
MDM2	E3 ubiquitin-protein ligase	2AXI
NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer	1IKN
PDGFA	Platelet-derived growth factor alpha chain	3MJK
PDGFB	Platelet-derived growth factor beta chain	3MJG
PIK3CA	Phosphatidylinositol-4, 5-Bisphosphate 3-kinase	3HHM
PTEN	Phosphatase and tensin homolog	1D5R
RB1	Retinoblastoma protein	2R7G
CCNDI	Cyclin D1-cyclin-dependent kinase 4	2W96
BCL2	B-cell lymphoma 2	2W3L
TGFA	Transforming growth factor alpha	1MOX
Anti-inflammatory receptors		
COX 1	Cytochrome C Oxidase 1	1Q4G
COX 2	Cytochrome C Oxidase 2	5F19
Anti-oxidant receptors		
SOD2	Manganese-dependent superoxide dismutase	2P4K
SOD3	Extracellular superoxide dismutase	2JLP
CAT	Catalase	1DGF

Source PDB database

Table 2: Pharmacokinetics prediction of the selected ligand using Pre-ADMET tool. Isoflavones showed better drug like features and pharmacokinetic properties with respect to daidzein, genistein and glycitein

Parameters	Daidzein	Genistein	Glycitein
ADME prediction			
Blood brain barrier	Middle absorption to CNS	Middle absorption to CNS	Low absorption to CNS
$CaCO_2$ permeability	Middle permeability	Middle permeability	Middle permeability
Human intestinal absorption	Well absorbed	Well absorbed	Well absorbed
Plasma protein binding	Weakly bound	Weakly bound	Weakly bound
Pure water solubility	High solubility	High solubility	Middle solubility
Drug likeness prediction			
CMC like rule	Qualified	Qualified	Qualified
Lead like rule	Suitable	Suitable	Suitable
MDDR like rule	Mid-structure	Mid-structure	Mid-structure
MDDR like rule violation fields	No rotatable bonds	No rotatable bonds	No rotatable bonds
Lipinski's rule	Suitable	Suitable	Suitable
Toxicity prediction mutagenicity			
Ames test	Mutagen	Mutagen	Mutagen
TA100_10RLI	Positive	Positive	Positive
TA100_NA	Positive	Positive	Positive
TA1535_10RLI	Negative	Negative	Negative
TA1535_NA	Negative	Negative	Negative
Carcinogenicity			
Mouse	Negative	Negative	Negative
Rat	Positive	Positive	Positive

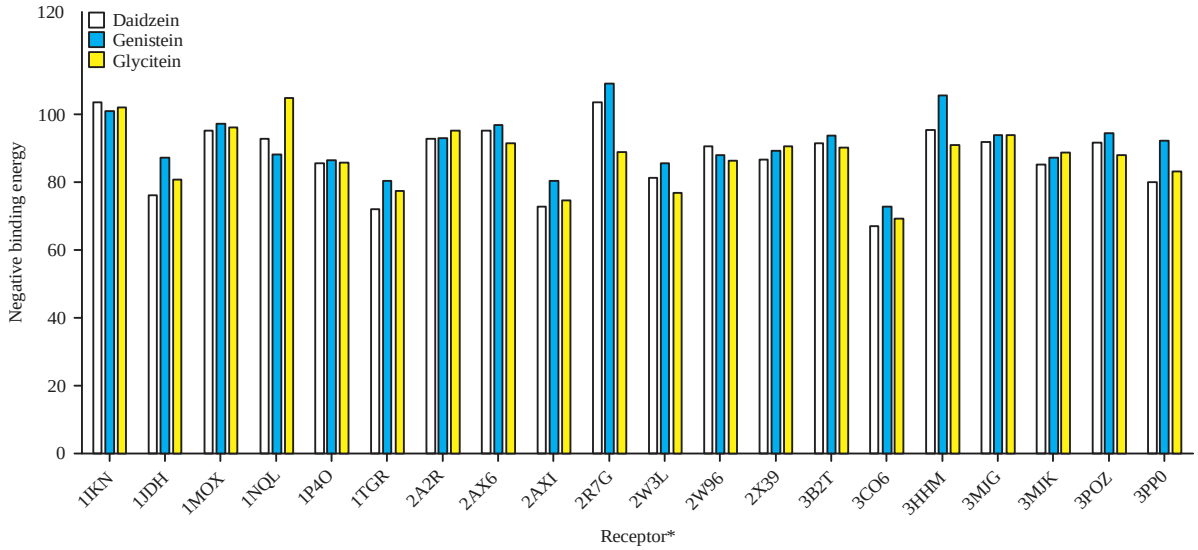

Fig. 1: Molecular docking studies of isoflavones with cancer drug targets showing negative binding energy

and toxicity predictions were performed. Daidzein, glycitein and genistein were predicted to have enhanced the pharmacokinetic features. ADME prediction for the three isoflavones showed favorable drug likeness properties with respect to $CaCO_2$.

Permeability, plasma protein binding predictions, CMC like rule and lipinki's rule. Toxicity predication parameters were found favorable for the drug likeness activity for the ligands. Through toxicity predication showed that three isoflavones as mutagenic levels at which they act as mutagen will be the determining factor. As reported by Mahajanakatti *et al.*[21], a safe molecule triterpene was shown mutagen. But the level at which it assumes the role is much higher than the physiological level that can be reached under *in vivo* condition. Hence the aspect of mutagenic nature of isoflavone through this prediction needs relook by *in vivo* experiments. The drug likeliness properties and pharmacokinetic features are shown in Table 2.

Prediction of *in silico* anti-cancer properties of daidzein, genistein, glycitein: Multi receptor docking was performed to analyse the inhibitory action of Daidzein, Genistein and Glycitein with the various cancer receptors that were considered as probable drug targets. The best-docked conformations were selected based on the lowest docking energy (binding energy) of docked complexes, number of interacting residues and number of hydrogen bonds. Genistein showed the highest energy of interaction amongst the isoflavones in most docking poses (Fig. 1). Five main receptors, EGF, NFKBIA, PIK3CA, PTEN and RB1 showed best binding interactions (Fig. 2). The binding energies of docked complex were found to be -103.59, -90.675, -100.73, -105.68 and -109.2 kcal mol^{-1}, respectively. Previous researchers have shown several cancer target viz the Epidermal Growth Factor (EGF) acting as potential drug targets for gastric cancer[23]; Nuclear factor of kappa (NFKBIA)[24] in B-cells inhibition of Hodgkin lymphoma pathway; (PIK3CA) phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit responsible in Ovarian Cancer pathway. (PTEN) phosphatase and tensin; Retinoblastoma 1 (RB1) to have major functionality in Small cell lung cancer, prostate cancer, endometrial cancer, vulvar cancer, breast cancer, malignant melanoma, glioma, hepatocellular carcinoma, Chronic myeloid Leukemia, oesophageal cancer, bladder cancer and osteosarcoma pathways[25]. We found the main residues interacting with EGF are ARG-48, ASN-49, LEU-52, GLU-73, TYR-50, VAL-72 and ARG-74 (Fig. 2a). For NFKBIA are LYS-79, HIS-181, GLN-29, PRO-182, PHE-184, ARG-187, THR-191, GLN-220, GLY-31, ASN-186, ALA-188, ARG-274, SER-276, ASP-277 and ARG-33 (Fig. 2b). For PIK3CA are SER-7, GLY-8, ARG-87, LYS-711 and ARG-87 (Fig. 2c). For PTEN are HIS-93, CYS-124, LYS-125, GLY-129,ARG-130,LYS-330,LYS-1[28] and THR-167 (Fig. 2d) For RB1 are ARG-552, ARG-661, GLU-559, HIS-699.LEU-731, PRO-732, HIS-733 and ALA-734 (Fig. 2e). From our study, it is evident that isoflavones have wide range of inhibitory properties against various cancer drug targets. Superior inhibitory properties and ideal pharmacokinetic features make isoflavones as an ideal inhibitor and therapeutic substances against extensive varieties of cancer. Though, present data is mainly based on computer aided virtual screening, our data would pave significant insights for such kinds of studies.

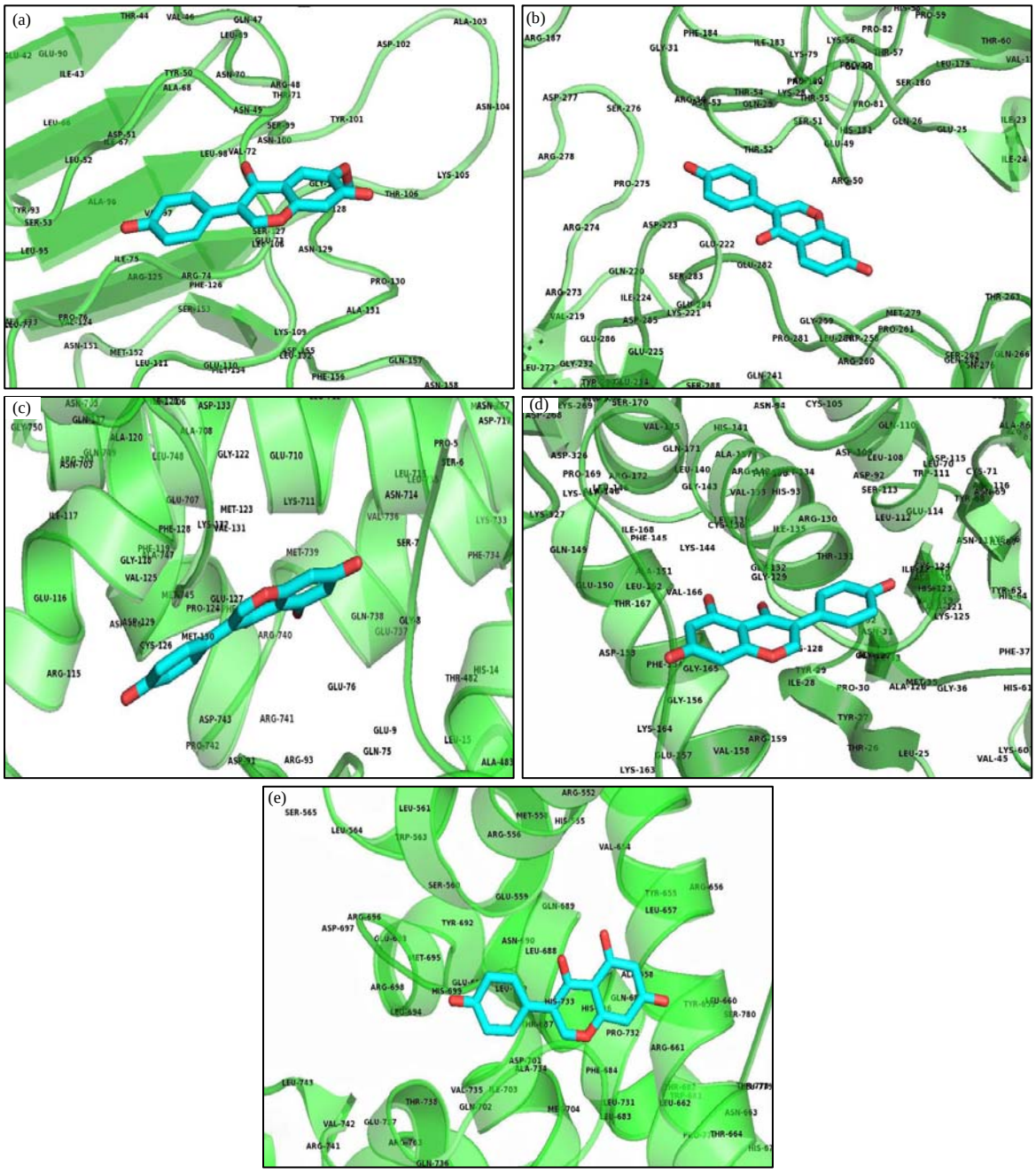

Fig. 2(a-e): Binding interaction of specific receptor target with daidzein, genistein and glycitein, (a) Epidermal growth factor(EGF), (b) Nuclear factor of kappa (NFKBIA), (c) Phosphatidylinositol 4,5-Bisphosphate, (d) Phaosphatese and tensin (PTEN) and (e) Retinoblastoma (RB1)

Prediction of *in silico* anti-inflammatory property of daidzein, genistein and glycitein: Presuming anti-inflammatory property of isoflavones, it is studied that docking interactions with COX-1 and COX-2 gene products. Isoflavones had apparently high interactions with the drug receptors. Genistein has an enhanced effect against anti-inflammatory properties where showing the highest interaction among the isoflavones molecules (Fig. 3). COX1 receptor showed best binding interaction with genistein. The binding energies of docked complex were found to be -110.38, -116.48 and -104.35 kcal mol^{-1} for daidzein, genistein and glycitein, respectively. The main residues of interactions

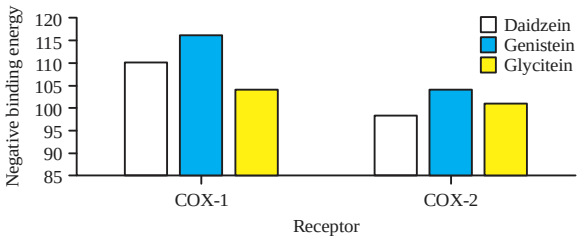

Fig. 3: Molecular docking studies of isoflavones with anti-inflammatory drug target showing negative binding energy

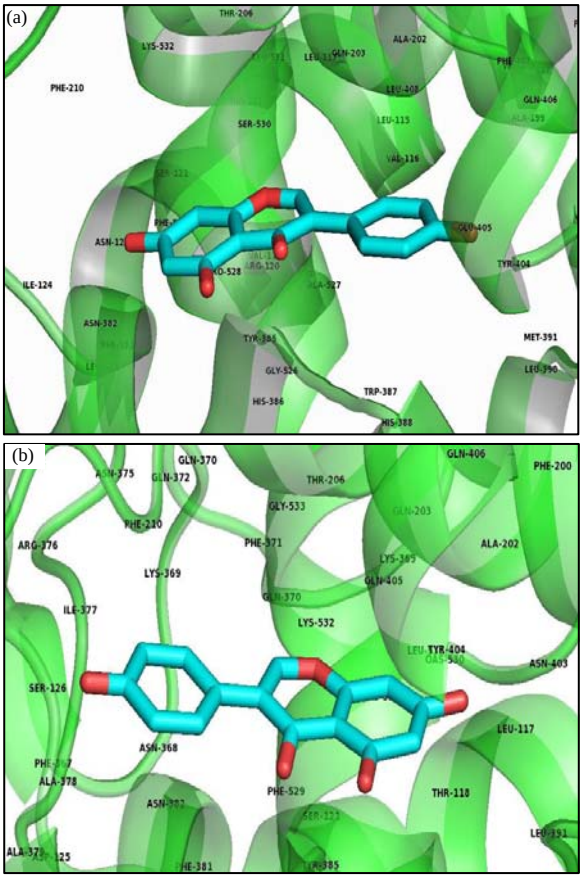

Fig. 4(a-b): Binding interaction of COX-1 and COX-2 receptors with genistein, (a) Cyclooxygenase 1 receptor (COX-1) and (b) Cyclooxygenase 2 receptor (COX-2)

for COX1 were, GLN-44, GLN-42, HIS-43, THR-206, ASN-382, ALN-203, GLN-203, HIS-207, PHE-210, HIS-388, LYS-468, ARG-469 (Fig. 4a) and for COX2 were, ALA-202, GLN-203, THR-206, HIS-207, PHE-210, ASN-382, TYR-385, THR-212, HIS-388, HIS-214, HIS-386, TRP-387 (Fig. 4b) All the isoflavones were subjected to *in silico* molecular modeling with anti-inflammatory (COX-2 receptor) targets. COX-1 and

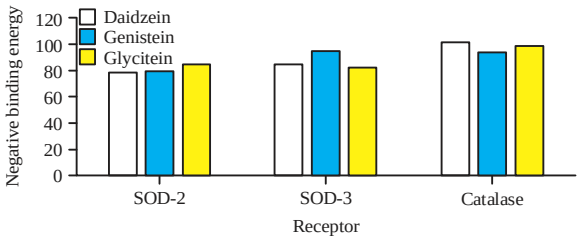

Fig. 5: Molecular docking studies of isoflavones with antioxidant proteins showing a negative binding energy

COX-2 are expressed under normal conditions in the human body which have physiological and immunological activity in some tissues viz cytoprotection of gastrointestinal tissues and platelet aggregation by COX-1; fundamental function of the brain by COX-2 and immunore activities in brain by both COX-1 and COX-2[26]. However, besides vital activity in the brain, COX-2 plays an important role in the inflammation scenario in response to cytokines and pro-inflammatory molecules. Pendota *et al.*[27] reported the *in silico* studies of anti-inflammatory and antioxidant in *Buddleja salviifolia* they have found the highest binding affinity (dock score of 92.18 and 68.93 kcal mol^{-1}) and good hydrogen bond interactions in catalytic site of COX-2.

Prediction of *in silico* anti-oxidant property of daidzein, genistein and glycitein: Daidzein, genistein and glycitein were subjected to docking studies with three receptors-catalase, SOD-2 and SOD-3. This was based on the speculation that isoflavones are known to increase the mRNA expressions and activities of superoxide dismutase (SOD) and catalase[28]. Each of the isoflavones under investigation have shown different interactions between the chosen receptors (Fig. 5). Catalase showed highest binding interactions. The binding energies of docked complex were found to be -100.665, -94.0288, -97.5342 kcal mol^{-1} for daidzein, genistein and glycitein respectively The Interaction residues for Catalase were ARG-72, ARG-112, TYR-358, HIS-75, GLY-147, ASN-148, PHE-153, ARG-354, TYR-358, ASP-389, ASN-403, ARG-68, GLU-330, GLU-71, GLU-119 and ARG-170 (Fig. 6a). For SOD2 were PHE-66, ASN-142, ASP-144, VAL-118, GLN-119, PRO-141, PHE-66, SER-3, HIS-71, SER-75, VAL-54, THR-55, HIS-2, PRO-5, HIS-71 and ILE-72 (Fig. 6b). For SOD3 ALA-55, ARG-59, ALA-51, LEU-53, ASP-54, ARG-158, SER-154, VAL-156 and VAL-194 (Fig. 6c). Hence probably catalase was the best target for antioxidant activity however we cannot rule out the role of SOD-2 and SOD-3 as antioxidant target. Moreover all the three isoflavones had similar influence on the three receptor studied.

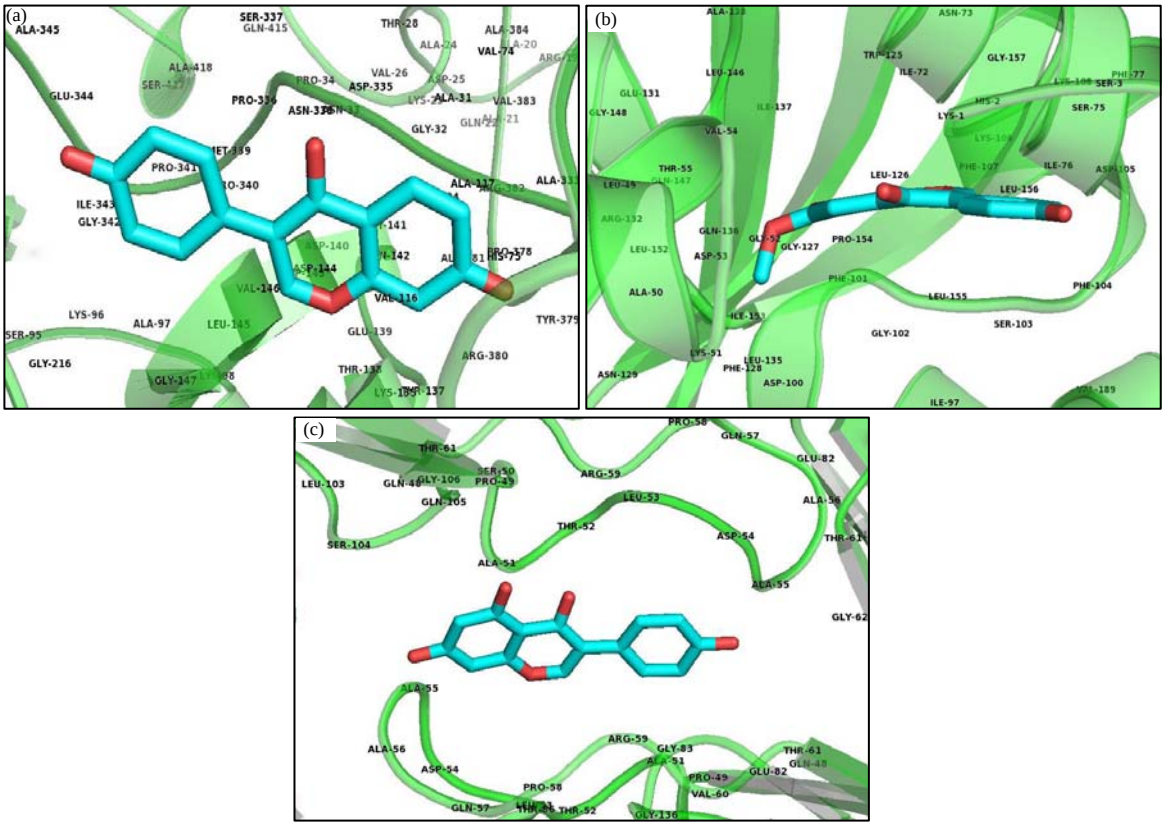

Fig. 6(a-c): Binding interaction of COX-1 and COX-2 receptors with daidzein, genistein and glycitein, (a) Catalase, (b) Super oxidase dismutase 2 (SOD2) and (c) Super oxidase dismutase 3 (SOD3)

CONCLUSION

Isoflavones is a chief component of legumes which exhibit antioxidant, anti-inflammatory, anti-microbial and anti-carcinogenic activities. Present study revealed that the inhibitory properties of isoflavones against various cancer drug targets by computer aided virtual screening. Computer aided predictions showed that isoflavones was an ideal drug candidate with better drug likeness and pharmacokinetic properties. This comparative study revealed that isoflavones showed better inhibitory activities against the virulent gene products of epidermal growth factor (EGF), Platelet-derived growth factor receptor (PDGFA) and Glutathione S-transferase pi gene (GST-PI) than their native ligands. COX-1 protein was successfully docked onto daidzein, genistein and glycitein for drug interaction studies with best binding energy showing the significance of COX 1 as anti-inflammatory target by isoflavones. As similarly isoflavones showed best binding against catalase receptors. Present data cover crucial landmarks for further studies to validate isoflavones as promising drug candidate against various cancers.

SIGNIFICANT STATEMENT

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

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REFERENCES

1. Sinclair, T.R., L.R. Salado-Navarro, G. Salas and L.C. Purcell, 2007. Soybean yields and soil water status in Argentina: Simulation analysis. Agric. Syst., 94: 471-477.
2. Anthony, M.S., T.B. Clarkson, C.L. Hughes, Jr., T.M. Morgan and G.L. Burke, 1996. Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. J. Nutr., 126: 43-50.
3. Kennedy, A.R., 1998. Chemopreventive agents: Protease inhibitors. Pharmacol. Therapeut., 78: 167-209.
4. Kreijkamp-Kaspers, S., L. Kok, D.E. Grobbee, E.H. de Haan, A. Aleman, J.W. Lampe and Y.T. van der Schouw, 2004. Effect of soy protein containing isoflavones on cognitive function, bone mineral density and plasma lipids in postmenopausal women: A randomized controlled trial. J. Am. Med. Assoc., 292: 65-74.
5. Friedman, M. and D.L. Brandon, 2001. Nutritional and health benefits of soy proteins. J. Agric. Food Chem., 49: 1069-1086.
6. Michelfelder, A.J., 2009. Soy: A complete source of protein. Am. Fam. Physician, 79: 43-47.
7. Xiao, C.W., 2008. Health effects of soy protein and isoflavones in humans. J. Nutr., 138: 1244S-1249S.
8. Wang, Q., X. Ge, X. Tian, Y. Zhang, J. Zhang and P. Zhang, 2013. Soy isoflavone: The multipurpose phytochemical. Biomed. Rep., 1: 697-701.
9. Yu, J., X. Bi, B. Yu and D. Chen, 2016. Isoflavones: Anti-inflammatory benefit and possible caveats. Nutrients, Vol. 8. 10.3390/nu8060361.
10. Dower, J.I., J.M. Geleijnse, L. Gijsbers, P.L. Zock, D. Kromhout and P.C. Hollman, 2015. Effects of the pure flavonoids epicatechin and quercetin on vascular function and cardiometabolic health: A randomized, double-blind, placebo-controlled, crossover trial. Am. J. Clin. Nutr., 101: 914-921.
11. Grace, M.H., D. Esposito, K.L. Dunlap and M.A. Lila, 2013. Comparative analysis of phenolic content and profile, antioxidant capacity and anti-inflammatory bioactivity in wild Alaskan and commercial *Vaccinium* berries. J. Agric. Food Chem., 62: 4007-4017.
12. Al-Anazi, A.F., V.F. Qureshi, K. Javaid and S. Qureshi, 2011. Preventive effects of phytoestrogens against postmenopausal osteoporosis as compared to the available therapeutic choices: An overview. J. Nat. Sci. Biol. Med., 2: 154-163.
13. Cavallini, D.C.U., J.Y. Suzuki, D.S.P. Abdalla, R.C. Vendramini and N.D. Pauly-Silveira *et al.*, 2011. Influence of a probiotic soy product on fecal microbiota and its association with cardiovascular risk factors in an animal model. Lipids Health Dis., Vol. 10. 10.1186/1476-511X-10-126.
14. Nagata, C., 2010. Factors to consider in the association between soy isoflavone intake and breast cancer risk. J. Epidemiol., 20: 83-89.
15. Berman, H.M., J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig and P.E. Bourne, 2006. The Protein Data Bank, 1999-2017. In: International Tables for Crystallography Volume F: Crystallography of Biological Macromolecules, Rossmann, M.G. and E. Arnold (Eds.)., Springer-Verlag, German, pp: 675-684.
16. Kanehisa, M. and S. Goto, 2000. KEGG: Kyoto encyclopedia of genes and genomes. Nucl. Acids Res., 28: 27-30.
17. Zarghi, A. and S. Arfaei, 2011. Selective COX-2 inhibitors: A review of their structure-activity relationships. Iran. J. Pharm. Res., 10: 655-683.
18. Daisy, P., S. Suveena and R.C.R. Latha, 2012. Target level analysis of antioxidant activity of costunolide and eremanthin isolated from *Costus* speciosus. Asian J. Pharm. Clin. Res., 5: 32-35.
19. Pence, H.E. and A. Williams, 2010. ChemSpider: An online chemical information resource. J. Chem. Educ., 87: 1123-1124.
20. Seal, A., R. Aykkal, R.O. Babu and M. Ghosh, 2011. Docking study of HIV-1 reverse transcriptase with phytochemicals. Bioinformation, 5: 430-439.
21. Mahajanakatti, A.B., G. Murthy, N. Sharma and S. Skariyachan, 2014. Exploring inhibitory potential of Curcumin against various cancer targets by *in silico* virtual screening. Interdiscip. Sci.: Comput. Life Sci., 6: 13-24.
22. Hsu, K.C., Y.F. Chen, S.R. Lin and J.M. Yang, 2011. iGEMDOCK: A graphical environment of enhancing GEMDOCK using pharmacological interactions and post-screening analysis. BMC Bioinform., Vol. 12. 10.1186/1471-2105-12-S1-S33.
23. Liu, K.W., B. Hu and S.Y. Cheng, 2011. Platelet-derived growth factor receptor alpha in glioma: A bad seed. Chinese J. Cancer, 30: 590-602.
24. Curran, J.E., S.R. Weinstein and L.R. Griffiths, 2002. Polymorphic variants of NFKB1 and its inhibitory protein NFKBIA and their involvement in sporadic breast cancer. Cancer Lett., 188: 103-107.
25. Chinnam, M. and D.W. Goodrich, 2011. RB1, development and cancer. Curr. Topics Devel. Biol., 94: 129-169.
26. Breder, C.D., D. Dewitt and R.P. Kraig, 1995. Characterization of inducible cyclooxygenase in rat brain. J. Comprehen. Neurol., 355: 296-315.
27. Pendota, S.C., A.R. Ndhlala, A.O. Aremu, M.A. Aderogba and J. Van Staden, 2014. Anti-inflammatory, antioxidant and in silico studies of *Buddleja salviifolia* (L). Lam leaf constituents. S. Afr. J. Bot., 93: 79-85.
28. Ma, X., Z. Jiang, J. Zhang, Y. Hu, K. Gao, L. Wang and X. Yang, 2015. Isoflavone ameliorates H_2O_2 induced injury by activating the antioxidant system of sow mammary gland cell. Natural Sci., 7: 571-580.