Molecular Docking Explains Atomic Interaction between Plant-originated Ligands and Oncogenic E7 Protein of High Risk Human Papillomavirus Type 16

Satish Kumar[1*], Lingaraja Jena[1], Sneha Galande[1], Sangeeta Daf[2], Ashok K. Varma[3]

[1]*Bioinformatics Centre & Biochemistry*
Mahatma Gandhi Institute of Medical Sciences
Sevagram, India
E-mails: satishangral@gmail.com, lingaraj.jena@gmail.com, snew.29@gmail.com

[2]*Datta Meghe Institute of Medical Sciences*
Deemed University
Nagpur, India
E-mail: sangeetadaf@gmail.com

[3]*Advanced Centre for Treatment*
Research & Education in Cancer
Kharghar, Navi Mumbai, India
E-mail: avarma@actrec.gov.in

[*]*Corresponding author*

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Abstract: *Cervical cancer caused by Human papillomavirus (HPV) is one of the leading causes of cancer mortality in women worldwide, particularly in the developing countries. In the last few decades, various compounds from plant origin such as Curcumin, Epigallocatechin gallate (EGCG), Jaceosidin, Resveratrol etc. have been used as anti cancer therapeutic agents. Different studies have shown these plant-originated compounds are able to suppress HPV infection. The E6 and E7 oncoproteins of high-risk HPV play a key role in HPV related cancers. In this study, we explored these ligands from plants origin against E7 oncoprotein of high risk HPV 16, which is known to inactivate tumor suppressor pRb protein. A robust homology model of HPV 16 E7 was built to foresee the interaction mechanism of E7 oncoprotein with these ligands using structure-based drug designing approach. Docking studies demonstrate the interaction of these ligands with pRb binding site of E7 protein by residues Tyr52, Asn53, Val55, Phe57, Cys59, Ser63, Thr64, Thr72, Arg77, Glu80 and Asp81 and help restoration of pRb functioning. This in silico based atomic interaction between these ligands and E7 protein may assist in validating the plant-originated ligands as effective drugs against HPV.*

Keywords: *Cancer, Docking, HPV-16, E7, Plant ligands.*

Introduction

Human papillomavirus (HPV) belongs to papillomavirus family, causes 5.2% of all cancers globally. HPV besides cervical cancer also causes a subset of anogenital, head and neck cancer [6, 13]. However, cervical cancer contributes most to cancer mortality in women worldwide with an estimated 49 300 diagnoses and 274 000 deaths annually [21]. Even though there are more than 200 types of HPV identified, the most common associated with cervical cancer are “high-risk” HPV-16 and HPV-18, responsible for about 62.6% and

15.7% of cervical cancers respectively [12]. HPV-16 and HPV-18 remains the primary target for anti-cancer drug development. The E6 and E7 onco-proteins have been shown to interact specifically with the p53 and pRb tumor suppressor proteins, respectively [25]. The major function of E6 oncoprotein is degradation of p53, inactivating the p14ARF-p53 pathway, while E7 promotes the degradation of pRb [8]. Both pRb and p53 negatively regulate the cell cycle, and also appear to inhibit G0-G1 and G1-S phase transitions. These interactions apparently play important roles in the induction of cell immortality.

The HPV E7 protein is a multifunctional oncoprotein [3] which induce terminally differentiated cells to enter the cell cycle. This small nuclear phosphoprotein, is known to interact with the product of the retinoblastoma susceptibility locus (pRb) and the related pocket protein family members p107 and p130 [9]. The interaction of E7 with pRb is crucial for transformation and abrogation of the anti-proliferative signals in cervical cancer [10, 22].

Since three decades, HPV is known as a causative agent for cervical cancer, but still the effective treatment against HPV infection is unavailable [4]. In recent years, different plant-originated compounds have been identified as promising sources of drugs for therapeutic and prophylactic use in cancer [11].

Resveratrol (trans-3,5,4′-trihydroxy-trans-stilbene), usually found in nuts, grapes, berries and red wine is a natural polyphenolic phytoalexin compound [7]. This compound along with cisplatin or doxorubicin has been shown as an additive growth-inhibitory anticancer effect on uterine cancer cells [24]. Bava et al. [2] showed that curcumin sensitizes cervical cancer cells to the therapeutic effect of taxol, acting in the down-regulation of both NF-κB and serine/threonine kinase AKT pathway, a survival signal related to NF-κB. Curcumin is cytotoxic to cervical cancer cells in a time- and concentration dependent manner and when applied, the cytotoxicity was found to be higher in HPV infected cells [2]. Moreover, it was shown that curcumin down regulates the expression of E6 & E7 proteins of HPV-16 resulting in loss of the transforming phenotype and the cessation of cellular growth. Singh and Singh [26] explored other molecular mechanisms exerted by curcumin in cervical cancer cells and found that it inhibits telomerase activity, RAS and ERK signaling pathway, cyclin D1, COX-2 and iNOS activity [26]. EGCG [(-)-epigallocatechin-3-gallate], the most abundant and active tea catechin, has been found to have antiviral and antitumor properties; in patients with HPV infected cervical lesions [1]. Qiao et al. [23], has shown an inhibitory effect of EGCG on the growth of CaSki (HPV-16 positive) and HeLa (HPV-18 positive) cells in a time- and concentration dependent manner and also on the expression of HPV E7 [23]. Lee et al. [19] isolated Jaceosidin from the methanol (MeOH) extract of *Artemisia argyi* and reported its inhibitory effects on binding between E7 oncoproteins and the Rb tumor suppressor protein.

We have carried out molecular modeling studies on E6 and E7 proteins of HPV strains [16] followed by computational docking analysis with natural inhibitors of HPV-16 E6 protein [17] previously. The purpose of this present study was to explicate the atomic interaction between plant-originated ligands and high risk HPV-16 E7 oncogenic protein. In this study, three dimensional structure of E7 protein of HPV type 16 was modeled using Phyre 2 server and structural refinement and energy minimization was performed by YASARA (Yet Another Scientific Artificial Reality Application) energy minimization server. Docking analysis was performed using AutoDock tool to reveal the interaction between HPV E7 oncoprotein with the ligands.

Materials and methods

HPV-16 E7 protein

E7 protein of Human papillomavirus type 16 was selected as drug target. The protein sequence of HPV-16 E7 (GenBank ID: AAD33253.1) was retrieved from NCBI platform (http://www.ncbi.nlm.nih.gov/).

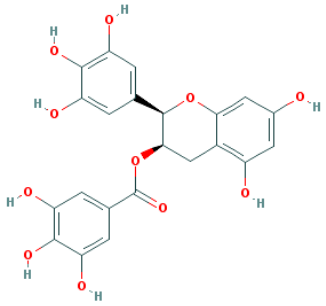
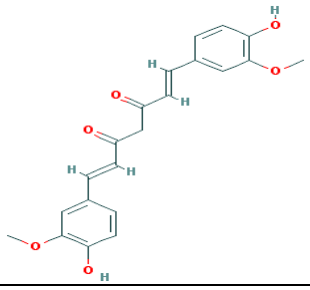
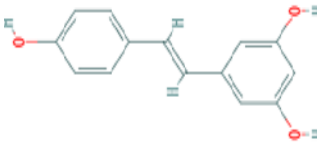
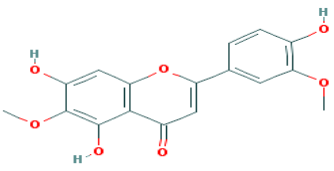
Protein structure prediction and validation of drug target

Phyre 2 server [14] was used for modeling of the three dimensional structure of E7 protein. YASARA Energy Minimization Server was used for structural refinement and energy minimization of the predicted model [15]. The refined model reliability was assessed through Procheck [18], ProSA-web [30] and Protein Quality Predictor (ProQ) [28]. The refined model was further verified by ERRAT server [5].

Ligand preparation

Chemical structures of plant-originated compounds (Curcumin, EGCG, Jaceosidin, Resveratrol, Withaferin A) were retrieved from PubChem database [29] (Table 1).

Table 1. Plant-originated compounds applied for treatment and prevention of cancer

Compound name	Structure	Molecular weight, (g/mol)
EGCG: [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate		458.37172
Curcumin: (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione		368.3799
Resveratrol: 5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol		228.24328
Jaceosidin: 5,7-Dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-6-methoxy-4H-chromen-4-one		330.28886

Protein-ligand docking

Protein-ligand docking studies were performed using one of the most widely used software AutoDock 4.2 program [20]. All the pre-processing steps for ligand and protein files were performed using AutoDock Tools 1.5.4 program (ADT) which has been released as an extension suite to the Python Molecular Viewer [20]. ADT program was used to prepare receptor molecule (HPV-16 E7) by adding all hydrogen atoms into carbon atoms of the receptor and assigning Kollman charges. For docked ligands, non-polar hydrogens were also added. Gasteiger charges assigned and torsions degrees of freedom were allocated by ADT program.

The Lamarckian genetic algorithm (LGA) was applied to model the interaction pattern between E7 oncogenic protein and selected inhibitors. The grid maps representing the receptor proteins in the docking process were calculated using AutoGrid (part of the AutoDock package). A grid of 50, 50 and 50 points in *x*, *y*, and *z* directions was centered on the pRb binding sites of E7 proteins. For all docking procedures, 100 independent genetic algorithm runs with population size 150 were considered for each molecule under study. A maximum number of 25×105 energy evaluations; 27000 maximum generations; a gene mutation rate of 0.02 and a crossover rate of 0.8 were set for LGA. Autodock program was run in order to prepare corresponding docking log file (DLG) for further analysis.

Visualization

The visualization of structure files was done using graphical interface of ADT tool.

Results and discussion

Tertiary structure modeling and validation

E7 protein of Human papillomavirus type 16 has 98 amino acids in its protein sequence. Since three dimensional structure of E7 was not available, it was modeled using Phyre 2 server by taking the solution structure of HPV45 oncoprotein E7 (PDB ID: 2EWL) as template with confidence of 99.8%. The query coverage of target-template alignment was 51% with 40% identity (Fig. 1). The predicted structure was subjected to YASARA Energy Minimization Server for structural refinement. The total energy for the refined structure obtained was − 5918.7 kcal/mol (score: -1.08), while prior to energy minimization, it was 183.8 kcal/mol (score: -4.19).

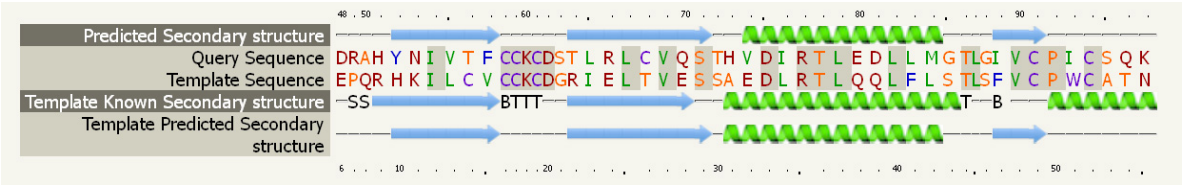


Fig. 1 Alignment between target (HPV-16 E7) and template (2EWL) along with predicted secondary structure obtained from Phyre 2 server

The stereochemistry of the refined model (Fig. 2A) (Procheck analysis) revealed that 83.7% residues were situated in most favorable region of the Ramachandran plot (Fig. 2B). ProSA-web evaluation revealed a compatible Z score (Fig. 2C) value of -2.56 which is well within the range of native conformations of crystal structures [30]. The overall residue energies of the E7 3D model were quite negative except for one peak (Fig. 2D). The 3D model of HPV 16 E7 protein showed LG score of 0.476 by ProQ tool [28]. Similar assumptions were achieved using the ERRAT plot (Fig. 2E), where the overall quality factor was 95%. All these outcomes recommended the reliability of the proposed model.

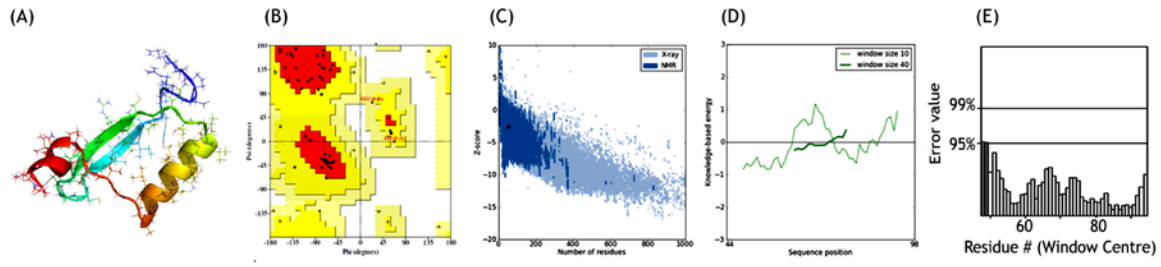


Fig. 2 (A) 3D structure of predicted HPV-16 E7 model; (B) Ramachandran plot of predicted E7 model; (C) ProSA-web Z-scores of all protein chains in PDB determined by X-ray crystallography (light blue) and NMR spectroscopy with respect to their length. The Z-score of E7 was present in that range represented in black dot; (D) Energy plot for the predicted E7 of HPV-16; (E) ERRAT plot for residue-wise analysis of homology model

Docking analysis of HPV-16 E7 with plant-originated ligands

As all the natural ligands (inhibitors) were found to be docked in various conformations and with varying binding energy, only the lowest energy conformation was considered. Upon the docking, complexes of the modeled structures of E7 oncoprotein and these ligands with high ranked binding energies are given in Table 2. 11 amino acid residues of HPV 16 E7 protein, i.e. Tyr52, Asn53, Val55, Phe57, Cys59, Ser63, Thr64, Thr72, Arg77, Glu80 and Asp81 contributed to pRb binding site. Active site of the model was analyzed based on the docking interaction of E7 with pRb binding site with all the 4 ligands.

Table 2. Polar contacts information from docking calculation between ligands and protein

Ligands	Binding energy, (kcal/mol)	Inhibition constant, (μM)	Residues	Atoms	Distance, (A^o)
Resveratrol	-9.26	0.1636	Val55 Phe57	H(N)···O H(N)···O	2.096 2.239
Curcumin	-6.32	23.25	Phe57 Phe57 Ile89	O···H H(N)···O H(N)···O	1.715 2.235 2.185
Jaceosidin	-4.77	318.07	Phe57	H(N)···O	2.059
EGCG	-4.09	1010.00	Phe57 Phe57 Ile89	O···H H(N)···O H(N)···O	1.715 2.178 2.131

Fig. 3 shows docked pose of four ligand molecules with E7 protein with almost similar kind of docking results. The detailed interactions are given in Table 2. Each ligand interacts with receptor at pRb binding site. Amongst those 4 different ligands, Resveratrol showed lowest binding energy of -9.26 kcal/mol with inhibition constant of 0.1636 μM for protein-ligand complex. Resveratrol found to interact with the E7 residues Val55 and Phe57 by forming hydrogen bonds and was shown to have anticancer growth-inhibitory effect [24]. This docking study reveals that the block of HPV infection might be due the high binding affinity of Resveratrol towards pRb bind site of E7 protein. Curcumin, showed the second lowest binding energy of -6.32 kcal/mol and with inhibition constant of 23.25 μM. During docking with the receptor, hydrogen bond interactions were found with two E7

residues (Phe57 and Ile89) while other two compounds Jaceosidin and EGCG were also found to interact with E7 protein with binding energy of -4.77 and -4.09 kcal/mol respectively. Phe57 was the interacting residues of the receptor proteins with Jaceosidin whereas EGCG was found interacting with Phe57 and Ile89.

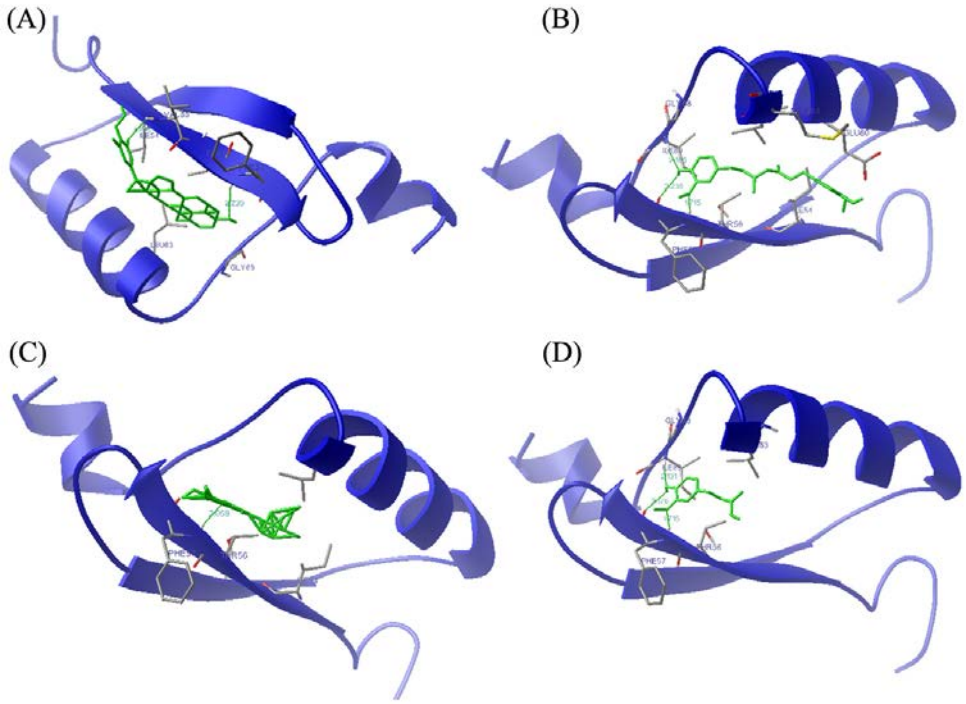


Fig. 3 Interaction profile of E7 with plant-originated ligands
(A) Resveratrol; (B) Curcumin; (C) Jaceosidin; (D) EGCG

All the plant-originated compounds were reported to inhibit HPV infection and our docking study also reveal – *in silico* validation of the inhibition. HPV-16 is known for causing high risk cervical cancer. Two ligands Resveratrol and Curcumin were found to interact with E7 oncoprotein of HPV-16 with significant binding energy and with the amino acid residues known for pRb binding. This interaction might prevent E7 protein to interact with host pRb protein, which may correlate why these compounds were used to treat HPV infections. Two other ligands, Jaceosidin and EGCG were also found forming the hydrogen bonds with pRb binding residues of E7 (Fig. 3C and Fig. 3D). This interaction might prevent E7 protein to interact with host pRb protein, which correlate why these natural compounds were found used to treat HPV infections.

Conclusion

Different plant-originated compounds have been identified and used as hopeful sources of drugs against cancer caused by HPV. Due to the advancement in bioinformatics and computational biology, validation of those natural drugs is possible through in silico approach. Inactivation of pRb is a common event in human cancer. It is also known to be inactivated directly by virally encoded oncoproteins like E7 of high risk HPV-16. Thus, E7 of HPV-16 may be of considerable interest for designing novel inhibitor to overcome the challenges of cervical cancer. A high-quality 3D model of E7 obtained through computational approach and docking analysis employing AutoDock 4.2 in this study provides high-throughput validation. This in silico approach may be of interest in designing new drugs from natural sources against cervical cancer.

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Prof. Satish Kumar, M.D.
E-mail: satishangral@gmail.com

Satish Kumar obtained MBBS from GMC, Jammu in 1990 and M.D. (Biochemistry) from Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sevagram, India in 1994. Presently he is a Professor in the Bioinformatics Centre & Biochemistry at the MGIMS. Prof. Kumar's activities and expertise: member of the Board of Studies in Biochemistry, Biotechnology & Bioinformatics, Maharashtra University of Health Sciences (MUHS), Nashik; member of the Scientific Advisory Committee, ICMR-NIC National Database on Indian Medical Journals; member & referee of the National Advisory Board, JK Science, Journal of Medical Education & Research; principal investigator on two CSIR funded projects on immunodiagnostics in tuberculosis and co-investigator on two UGC funded AMI and EPTB and one DBT funded project on BTISnet; patent on M tb ES-31 isolation process (184510/410/BOM/99/2001); coordinator on STP in Bioinformatics & Biotechnology; carrying out research work in immuno-detection of tuberculosis and structural & functional characterization of HPV; associate editor & publisher of the SEVAMED Quarterly Journal; convener of the Online Health Informatics Course & Moving Academy of Biomedical Communication; executive member of the Bioinformatics Centre, Raipur; convener of 16 workshops/CMEs on Medical Informatics & Biomedical Communication; recognized UG, PG and Ph.D. teacher of MUHS, Nashik; on panel of UG, PG & Ph.D. examination under many universities. Prof. Kumar has published 58 papers, 19 of which in international and 39 in national journals.

Lingaraja Jena, Ph.D.
E-mail: lingaraj.jena@gmail.com

Lingaraja Jena is a University Gold Medalist in M.Sc. (Bioinformatics) from Orissa University of Agriculture & Technology, Bhubaneswar, Odisha, India in 2006. Presently he works as an information officer in the Bioinformatics Centre & Biochemistry at the MGIMS. His areas of interest are in the fields of Development of Biological Database & Management, Programming, Bioinformatics Tools Application, Computational Biology, Sequence Analysis etc. Lingaraja Jena is continuing his work in the area of Sequence and Structure Analysis of *Mycobacterium tuberculosis* & HPV. He has published 11 research papers, 2 of which in national and 9 in international journals.

Sneha Galande, M.Sc.
E-mail: snew.29@gmail.com

Sneha Galande is a University Gold Medalist in M.Sc. (Bioinformatics) from Sant Gadge Baba Amravati University, Maharashtra, India in 2013. She is a recipient of DST inspire fellowship for pursuing Ph.D. Presently Sneha Galande is working as a Research Assistant at Bioinformatics Centre & Biochemistry, MGIMS, Sevagram, India. Her areas of interest are in the fields of Chemo-informatics, Drug designing, Genomics & Proteomics, Cancer Biology, Computational Biology, Sequence Analysis etc. Sneha Galande is continuing her work in the area of Sequence and Structure Analysis of HPV. She has published 2 research papers, 1 of which in national and 1 in international journals.

Prof. Sangeeta Daf, M.D.
E-mail: sangeetadaf@gmail.com

Sangeeta Daf obtained MBBS and M.D. (Obstetrics & Gynecology) from MGIMS, Sevagram in 1994 and 2001 respectively. Presently she serves as a Professor & HOD, Obstetrics & Gynaecology, Datta Meghe Institute of Medical Sciences (Deemed University), Nagpur (DAGA Memorial Women & Child Care Hospital Unit), and as a Director of the Mother Care Hospital and Chief Consultant OBGY, Life Care Hospitals, Nagpur, India. Prof. Daf's activities and expertise: recipient of International Training on Sexual & Reproductive Health & Rights at Uppsala University, Sweden & Colombo; NTTC for Health Professionals at JIPMER, Pondicherry, India; master trainer of Emergency Obstetrics Care, International joint venture of JEPHIGO & FOGSI; able-bodied skilled in Obstetric Emergencies, Infertility, Gynecological Cancer, Endoscopy, Sexual & Reproductive Health etc.; Held responsibility of President and Secretary, SWOGS (under FOGSI); recognized teacher by MUHS, Nashik for teaching, supervising and examining students pursuing M.D. Obstetrics & Gynecology and MBBS courses. Prof. Daf has published 15 papers in national & international journals, delivered talks and also chaired sessions in more than 25 national & international conferences/symposia/CME.

Dr. Ashok K. Varma, Ph.D.
E-mail: avarma@actrec.gov.in

Ashok K. Varma obtained Ph.D. from Jiwaji University, Gwalior in 1998 in X-ray crystallographic studies of biomolecules. Presently he serves as P.I. & S.O “E” at Varma Lab, Tata Memorial Center, Advanced Center for Teaching, Research and Education in Cancer, Mumbai. His research area of interest are in the field of Molecular Biology, Proteomics, Protein Biochemistry, Structural Biology, Structure determination using MAD, SAD, MIR and Molecular Replacement methods, model building and refinement of protein structures, Structural Bioinformatics – Structure Based Drug Design, Molecular Modeling, QSAR, CoMFA. Ashok K. Varma has published 16 papers in national and international journals.