EFFECT OF POLYPHENOLIC COMPOUNDS ON THE REGULATORS OF AUTOPHAGY

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CANDIDATE'S DECLARATION

I Pooja, Roll Number: 2K20/MSCBIO/20, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled — **EFFECT OF POLYPHENOLIC COMPOUNDS ON AUTOPHAGY REGULATORS** in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is an authentic record of my own carried out during the period from January- May 2022, under the supervision of Dr. Asmita Das.

Date: 6th May 2022

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CERTIFICATE

To the best of my knowledge, the above work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere. I further certify that the publication and indexing information given by the student is correct.

Place: Delhi

Date: 6th May 2022

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ABSTRACT

Autophagy is a self degradative process in which certain organelles, which are damaged, incorrectly folded or aggregated proteins and some intracellular pathogens undergo lysosome mediated enzymatic degradation. Loss of regulation of autophagy can result into certain pathophysiological conditions such as neurodegenerative diseases, cardiovascular disease and cancer. Autophagy plays two roles in cancer, tumor suppression at initial benign stage and tumor progression in established tumors. While Apoptosis is a natural process where cells that are no longer required can be eliminated in a highly regulated, controlled manner. When the apoptotic pathways are impaired or are not tightly regulated, autoimmune diseases, inflammatory diseases, viral and bacterial infections and cancers ensue. Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. Polyphenols are produced in plants as secondary metabolites due to various kinds of stress. These polyphenolic compounds have the ability to induce cancer cell death via apoptosis and can prevent cancer cell progression. As mentioned, autophagy also plays role in cancer prevention. Hence, the objective of project was to see the effects of selected polyphenols (Quercetin, Curcumin & Resveratrol) on the regulators of autophagy like Atg7, ULK1, AMPK etc. with the help of docking. To see whether they can act as anticancer agents via inducing both the processes.

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CHAPTER 1: INTRODUCTION

Cancer is the second driving wellbeing concern on the grounds that its commonness is expanding worldwide and there are at present no viable medicines. Current malignant growth medicines in light of chemo and radiotherapy make genuine side impacts. Thus, it is basic to foster other option or adjuvant methodologies. Plant-inferred food items are acquiring fame, attributable to one's prosperity and remedial possibility. Polyphenols are a class of natural mixtures that are for the most part regular and water solvent. Most investigations report that plant-determined polyphenols have numerous enemy of cancer-causing properties, remembering inhibitory impacts for disease cell multiplication, growth headway, tissue recovery, fiery reactions, and growth development by changing different biochemical pathways and elements engaged with tumorigenesis. The anticancer properties of polyphenolic mixtures, for example, quercetin, curcumin, and resveratrol have been concentrated in various disease cell lines. (Pritam Bhagwan Bhosale, 2020) Polyphenols are an assorted wellspring of auxiliary metabolites found in plants that assume significant parts in development, digestion, and security against Uv beams and various unsafe microscopic organisms. Polyphenols have been displayed to influence a few disease counteraction systems, including oxidation avoidance, xenobiotic detoxification, apoptosis acceptance, and estrogenic/against estrogenic movement.

Polyphenols are classified based on phenol rings as well as the primary parts that interface these rings. Phosphoric acids, phenolics, tannins, and flavonoids are among the gatherings. Polyphenols can: 1. smother the overexpression of favorable to oxidant enzymatic responses purportedly associated with growth movement; 2. repress record factor enactment, along these lines attempting to direct point qualities related in cell cycle movement; and 3. initiate apoptosis.4.Inhibit matrix metalloproteinases (MMPs) and epidermal development factor (VEGF), which are taken part in metastasis progression. The atomic premise of polyphenols' chemopreventive action is talked about, with accentuation on one's effects on the commencement of cell apoptosis.

Autophagy keeps up with cell limits by enclosing explicit sub - cell parts and manufactured things, though apoptosis makes up for the shortcoming by killing imperfect or upsetting cells (Fan and Zong, 2013). Autophagy eases back cancer development by eliminating free extreme edifices on o2 response species and Damage to dna all through cancer development (Lim, Hanif, and Chin, 2021). Apoptosis is a deep rooted strategy wherein a phone's parts are compacted into small unsaturated fat wires for social event by resistant framework, that additionally winds up killing cell garbage, obliterates harmful cells and infection cells, and eliminates cells for development to keep up with homeostasis in the body (Aoki, et al., 2020). d/or the indication of administrative protein. Polyphenols, as indicated by a developing collection of proof, can straightforwardly balance fluctuating parts of an apoptotic pathway and additionally the portrayal of proteins included, like the arrival of cytochrome c with resulting initiation of caspases-9 and caspase-3, the increment of caspases-8 and t-Bid levels, the down-guideline of Bcl-2 and Bcl-XL articulation, the improved articulation of Bax and Bak, and the adjustment of record The objective of the task was to utilize docking to examine the impacts of chosen polyphenols (Quercetin, Curcumin, and Resveratrol) on autophagy controllers like Atg7, ULK1, AMPK, and others. To decide if they can work as anticancer specialists by prompting the two cycles.

REVIEW OF LITERATURE

CHAPTER 2: AUTOPHAGY AND CANCER

2.1 What is autophagy?

Autophagy is an interaction that plays out an assortment of capacities like homeostasis, hostile to maturing, and giving endurance senses under unpleasant circumstances. It additionally safeguards cells from intracellular microbes, poisons, harmed organelles, and total proteins. Autophagy manages the pace of transformation and limits the gathering of genomic harm. Over than 30 related qualities (ATG) proteins have been recognized as being associated with autophagic cycles, for example, freight engulfment or sequestration by twofold layer vesicles called autophagosomes, which combination with lysosomes to complete freight debasement. B. Poisonous protein amassing, as well as harmed organelles, lipids, and nucleic acids, as well as microbes When lysosomal compounds corrupt a nucleotide, an amine corrosive, an unsaturated fat, or a nutrient, the items are recycled to the cytoplasm and reused for energy. When lysosomal compounds corrupt a nucleic corrosive, amine corrosive, unsaturated fat, or nutrient, the items are reused back to the cytoplasm and reused for energy, accordingly keeping up with homeostasis and staying away from metabolic pressure. The autophagy interaction is parted into a few phases: (a) Autophagosomal film commencement and nucleation (phagophore) (b) Elongation (c) autophagosome conclusion (d) autophagosome-lysosome development (e) diminishment by means of lysosomal proteins.

An assortment of stresses can cause the beginning stage, including record elements or supplements, absence of oxygen, peroxidation, and protein development.Different sections, in besides to the endoplasmic reticulum, go about as film givers, for example, the golgi, reusing endosomes, mitochondria, or plasma layers. Autophagy substrates can incorporate intracellular microbes, cytosol, harmed organelles, and proteins known as freight. Freight and autophagy freight receptors collaborate through ubiquitin on freight, and freight receptors cooperate with autophagy manufacturing plants by means of the LC-3 associating area. Syntaxin 17 (STX17), synaptosomal-related protein 29 (SNAP 29), and lysosome-related layer protein 2 (LAM) are instances of dissolvable N-ethylmaleimide-touchy part animating protein receptor (SNARE) proteins. At long last, hydrolysis eliminates autophagy freight from lysosomes, bringing about the reusing of product offerings like amino acids or unsaturated fats to the cytosol.

2.2 MOLECULAR MECHANISM AND REGULATION OF AUTOPHAGY

The autophagy process involves numerous signalling pathways and protein sequences. Autophagy is induced by stressful conditions such as nutrient deprivation (due to the higher amount of cell expansion in cancer cells), anticancer treatment, hypoxia, and the occurrence of any intracellular pathogen.

1.The mammalian objective of rapamycin (mTOR) quality has been connected to conditions like cell multiplication, stress, and disease movement. mTOR is an autophagy negative controller viewed as downstream of AKT and upstream of autophagy-related qualities, controlling autophagy initiation and restraint. At the point when mTOR is enacted (occurs in non-distressing circumstances), it obstructs autophagy on the grounds that it phosphorylates autophagy-related qualities required for autophagy commencement, in this way restraining autophagy. The designs that make mTOR are mTORC1 and mTORC2, and every complex fills an

alternate role and has an alternate limitation. Repressing mTOR flagging (which occurs during upsetting circumstances) enacts autophagy pathways**. ii) AMPK**:- AMP-enacted protein kinase (AMPK) is the mTORC1 controller. AMPK is actuated under upsetting circumstances bringing about low ATP and improved AMP and ADP; it restrains mTORC1 and helps with the induction of autophagy. **iii)ULK**:- Unc-51-like autophagy-enacting kinase (ULK) complex. Whenever the ULK complex is initiated, it advances toward the phagophore and enacts other multidomain edifices like the classIIIP13K Complex. The ClassIIIP13K Complex additionally manages autophagy beginning by creating phosphatidylinositol-3-phosphate (P13P**). iv) Beclin-1 (BCN-1)** is a constituent of classIIIP13K that guides in autophagosome stretching by drawing in different proteins**. v) ATGs**: a controller of the autophagosome prolongation step. Microtubule-related protein 1 light chain 3 (LC3) is utilized by ATG5-ATG12/ATG16L edifices to help phagophore development. vi) LC3 is associated with phagophore prolongation.

By ATG-4B-interceded cysteine cleavage, the Pro LC3B structure is changed over into the dynamic LC3B-1 structure. Then, at that point, by communicating with the phosphatidylethanolamine (PE), ATG3, ATG7, and E3 complex, LC3B-I is changed over into LC3B-II. The autophagosome's inward and external layers contain LC3B-II, which helps with substrate restricting. Mature autophagosomes meld with lysosomes to shape autolysosomes, and hydrolase compounds present in lysosomes debase sequestered freight.

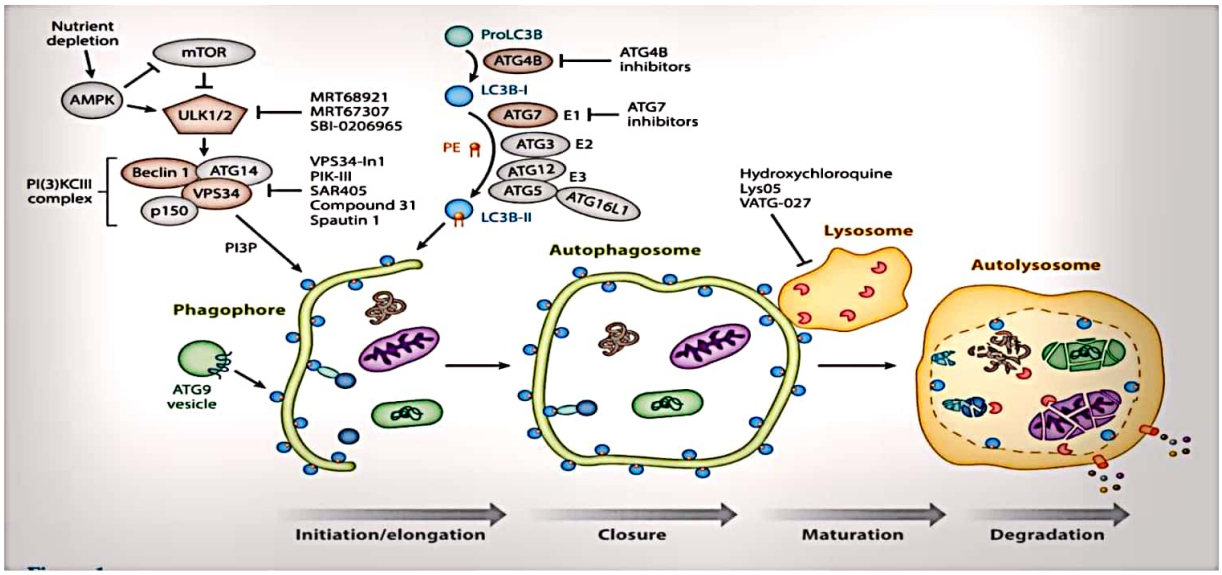

Figure 1 Molecular mechanism of autophagy (Naira Santana-Codina, 2017)

Initiation of autophagy and phagophore formation:-

Series of events take place starting from stressful conditions when AMPK gets activated, which inhibits mTORC1 and activates ULK complex. Activation of ULK is very important for initiation and nucleation, since it activates phosphatidylinositol 3-phosphate class III complex, It facilitate localisation of proteins on pre autophagosome, necessary for induction of autophagy.VPS34 gets activated upon phosphorylation by ULK complex, which in turn forms another complex made of ATG-14, VPS15 and beclin-1. During nucleation, beclin-1 recruits other proteins which are required for elongation. Phosphatidylinositol gets converted to phosphatidylinositol 3-phosphate(P13P) by VSP34, giving rise to phagophore.Anchoring of the P13K classIII complex through ATG-14 protein to omegasome facilitate this process to occur in endoplasmic

reticulum.

Elongation-It includes ATG5-ATG12 conjugation and LC3 processing, which then facilitates autophagosome formation. Atg7, E1 like enzyme, activates Atg12 in an ATP-dependent manner. Atg12 is then transferred to Atg10,E2 like enzyme, which mediates linkage of Atg12 to Atg5.This Conjugated form of Atg5–Atg12 complexes combines with Atg16L dimers and leads to formation of multimeric Atg5–Atg12–Atg16L complex which facilitates extension of phagophore. It helps in LC3 processing along with other Atgs(Atg4B, Atg7, Atg3) and phosphatidylethanolamine, PE, followed by closure of phagophore membrane and formation of autophagosome.Atg5–Atg12 conjugation is not dependent on activation of autophagy. Pro LC3B undergoes processing with Atg4B, a cysteine protease, converts it to LC3B-I and exposes glycine residue for the conjugation with PE and then it is activated by Atg7. To generate processed LC3B-II, activated form of LC3B-I is acted upon by Atg3, before conjugating with phosphatidylethanolamine (PE). Mature form of LC3B-II is recruited to growing isolation membrane and then binds to both sides including inner and outer surface of autophagosome. Distributed LC3B-II then helps in fusion with lysosomes and also recognise materials called cargo for degradation.

Lysosomal fusion and degradationdegradation:-Outer membrane of autophagosome fuses with lysosome and forming autolysosome involves 3 proteins;Rab GTPases, membrane-tethering factors and soluble N-ethylmaleimide-sensitive factor attachment proteins (SNAREs). Rab GTPases mediate recruitment of tethering complexes that bridge opposing lipid bilayers, which in turn recruit SNARE proteins to facilitate fusion of the autophagosome with the lysosome. Sequestered cargo undergoes degradation by lysosomal acid hydrolases. Salvaged nutrients are recycled and brought back to the cytoplasm for fulfilling energy requirements and thus maintaining homeostasis. Autophagy can also be regulated by cell cycle proteins and checkpoints

2.2. ROLE OF AUTOPHAGY IN CANCER

Autophagy plays a dual role in supporting oncosopressive cancer and tumors. Autophagy is mainly caused by phosphatidylinositol 3-phosphate kinase (PI3K) -AKT-MTOR signaling pathway (mammalian target of rapamycin). In the early stages of tumor development, autophagy acts as a tumor suppressor. In advanced stages of tumor development, autophagy promotes tumor progression. During later stages of cancer when tumor is established, tumor cells induce protective autophagy.

2.2.1.AUTOPHAGY IN TUMOR SUPPRESSION

Basal autophagy is believed to be a factor in cancer suppression.The primary level of autophagy acts as a mechanism to suppress the tumor. For example, the BECN1 gene, which is related to autophagy, encodes Beclin-1, which is important for phagophore formation and acts as a tumor suppressor. The role of autophagy as a mechanism of survival in normal and tumor cells manifests itself as an observational paradox that loss-of-function mutations in the autophagy pathway are associated with tumor progression. In addition, structural activation of the PI3K pathway is the most common development of human cancer and which prevents inclusion of autophagy under the influence of downstream MTOR kinase starvation. Initially, it was difficult to control how this or the loss of survival pathways via autophagy facilitates tumor ligation. However, there are two possibilities that are not mutually exclusive. One interpretation is that

it is a non-autonomous means of promoting intracellular tumors by providing a therapeutic response to necrotic cell death and inflammatory stimuli due to defects in apoptosis and autophagy. Another explanation is that due to the increased oxidative stress that can lead to disease progression, proper management of the metabolic stress of tumor cells is needed to suppress the formation of malignant mutations . Thus, overall cell viability is impaired by autophagy defects in tumor cells, but these early defects are due to increased mutation rates due to poor stress management of the anatomical cell line. This is consistent with how defective DNA repair is more susceptible to DNA damage, but the rate of change as a result of defective DNA repair leads to an increased incidence of tumorigenesis. Regulation of autophagy promotes expression of tumor suppression proteins. Tumor mitigation factors (negatively regulated by mTOR) induce autophagy and suppress cancer initiation. In contrast, the oncogene can be activated by mTOR, PI3K class I, and AKT, resulting in suppression of autophagy and increased cancer formation. Decreased and abnormal autophagy suppresses the breakdown of damaged components or proteins in cells exposed to oxidative stress, leading to the development of cancer. Basal autophagy is considered a cancer suppressant.

Oncosuppressive functions of autophagy: Suppression of lethal changes in autophagy has been suggested by several mechanisms: (1) maintenance of genetic / genomic stability, (2) disposal of endogenous sources of potentially mutant reactive oxygen species (ROS), (3) maintenance of common bioenergetic functions, (4) breakdown of oncogenic proteins, (5) cell-endogenous antiviral and antibacterial effects, (6) optimal activation of oncogene-induced senescence (OIS) and oncogene-induced cell death (OICD), (7) maintenance of a normal stem cell compartment, (8) many anti-inflammatory functions, (9) an important role in inducing and conducting immune surveillance against cancer.

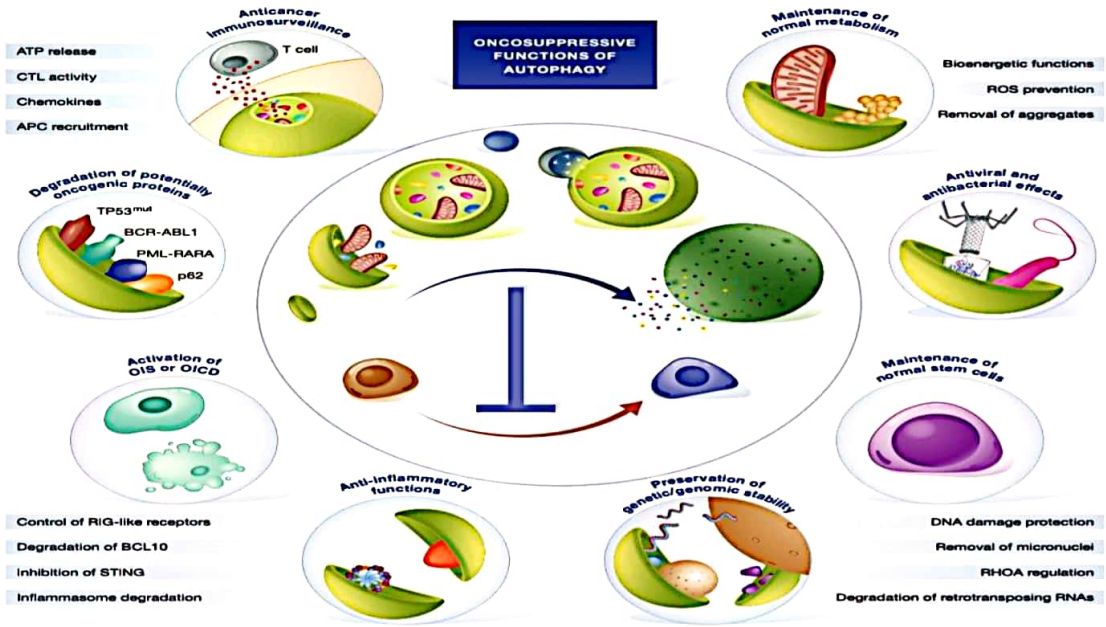

Figure 2 Oncosuppressive functions of autophagy (Lorenzo Galluzzi,2015)

Autophagy has been displayed to further develop antigen show by accelerating the exchange of microscopic organisms and proteins to lysosomes. To be sure, autophagy has been displayed to impact T cell-intervened interleukin (IL)- 17, interferon (IFN), and IL-22 creation in an IL-1

discharge subordinate way, demonstrating that autophagy is a vital controller of immunological reactions. The protein Atg5 is expected for B cell development. T lymphocyte endurance requires Atg7, in light of the fact that autophagy-lacking T lymphocytes produce more responsive oxygen species, probable because of deficient breakdown of metabolic subunits. Autophagy might improve disease analysis by advancing the partner T cell reaction. (Yunho Jin, 2017)

2.2.2.AUTOPHAGY IN TUMOR PROMOTION

Although autophagy may act as a suppressor of early tumorigenesis through several mechanisms, autophagic responses at later stages usually support the development and progression of constitutive tumors, along with reducing their susceptibility to internal stimuli. , As well as various treatments for microenvironmental stimuli that usually contribute to their death (promoting resistance). Autophagy can provide a survival mechanism under stressful conditions by removing damages and unnecessary molecules, which upon degradation can generate various precursors. Those precursors are recycled back to the cell, can act as substrate for energy production upon degradation. In cancer condition cells are rapidly dividing and increasing in number, which requires nutrients and energy for the survival which is provided by autophagy. Thus, autophagy helps in tumor survival and promote it. Tumors are subject to metabolic stress due to decreased blood supply, tumor vascular collapse, or medical intervention. Tumor cells are sensitive to metabolic stress, which is associated with a higher energy requirement for cell growth and a reduced ability to access nutrient-recycling activity via autophagy, so cancer cells reactivate autophagy Tumor-supporting functions of autophagy: Once a malignant transformation occurs, it is believed that or autophagy promotes tumor progression and resistance to treatment. These tumor support functions reflect the ability of autophagy to:

(1) increase the resistance of cancer cells to endocrine conditions that typically cause cell death, such as basement membrane detachment, hypoxia, and nutrient deprivation (2) mutations make cells less susceptible to therapy-induced cell death (3)Survival of cancer cells that enter a state of inactivity or numbness in response to treatment (4)ensuring cancer stem cell canister maintenance. EMT, epithelial mesenchymal transition

CHAPTER 3: APOPTOSIS AND CANCER

3.1 What is apoptosis?

Apoptosis is to be sure the cycle by which cells are modified to pass on. Eliminating bothersome cells during early development is utilized. Apoptosis is being utilized to purge the assemblage of harmed cells that can't be fixed. Apoptosis is additionally engaged with disease counteraction. Apoptosis in the core is portrayed by chromatin buildup and atomic discontinuity, as well as corralling of a cell, decline in cell volume (pyknosis), and withdrawal of pseudopodes. Chromatin buildup starts at the atomic layer's outskirts, attempting to frame a sickle or ring-like construction. The chromatin consolidates further till it separates within a cell with simply a flawless external layer, an interaction known as karyorrhexis. All through the whole cycle, the plasma layer stays in salvageable shape. A portion of the cells in the later phases of apoptosis. A few morphological elements of late apoptosis incorporate layer blebbing, ultrastructural alteration of cytoplasmic organelles, and a deficiency of film respectability. Regularly, phagocytic cells ensnare apoptotic cells before they structure apoptotic bodies. On the off chance that apoptotic cell leftovers are not phagocytosed, as in a fake cell lines environmental factors, they will start corruption like debasement, which is known as optional rot.

3.2.Apoptosis pathways:

Members of the passing receptor superfamily, like Fas, actuate the extraneous and demise receptor pathway (left). Structures a complex of Fas-L to Fas brings about receptor trimerization, work of explicit coactivators (FADD), and, accordingly, recruiting of procaspase 8 substances. The multi-atomic complex (Disk) enacts caspase-8, which can be restrained by c-FLIP. Dynamic caspase-8 can then initiate Bid, a Bcl-2 family protein that advances apoptosis, demonstrating a cross - talk among outward and inherent pathways. The natural pathway can be initiated by oxidants, poisons, sedates, or ionizing radiation, all of which cause ROS overproduction and stress flagging (right). DNA harm additionally enacts the inherent and mitochondrial course through p53 exercises. The passing upgrades make mitochondrial film respectability be lost and the arrival of cytochrome c, Apaf-1, and some other supportive of apoptotic viewpoints in the cytoplasm. The support or disturbance of mitochondrial film not set in stone by the proportion of favorable to apoptotic (Bax) to against apoptotic (Bcl-2) individuals from the Bcl-2 family, which causes or forestalls cythocrome c delivery. Various substances of cythocrome c, Apaf-1, dATP, and procaspase-9 tie together to frame an apoptosome, which enacts caspase-9 by means of autocatalysis. Caspase-9 and caspase-8 both sever procaspase-3, bringing about dynamic caspase-3, which then, at that point, animates other agent caspases and separates cell points. The Blockers of Apoptosis Protein (IAPs) family directs caspase action.

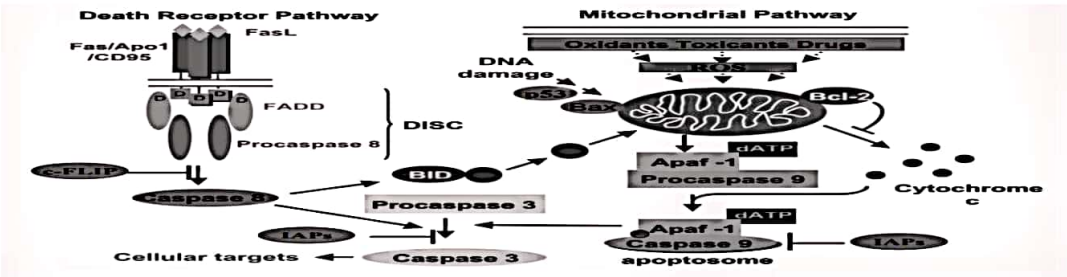

Fig 3: Apoptosis Pathways (Massimo D'Archivio, 2008)

3.3.How apoptosis prevents cancer?

Uncontrolled development, angiogenesis, and apoptosis avoidance are qualities of disease cells, no matter what the reason or type. One of the essential elements of apoptosis is malignant growth counteraction. Decline of apoptotic control permits carcinoma cells to develop longer, giving additional opportunity for transformations to aggregate, which can increment obtrusiveness during cancer development, improve angiogenesis, liberate cell multiplication, and disrupt separation. The most widely recognized strategies for avoidance are the raised degrees of antiapoptotic BCL-2 proteins as well as the deficiency of BAX and additionally BAK. BCL-2 isn't a sign of disease, however hereditary changes in it advance cancer commencement. Overexpression of the BCL-2 protein is seen as in the greater part, everything being equal, no matter what the sort. Thus, cancer cells become invulnerable to any inherent apoptotic boosts, including a few anticancer medications. Numerous anticancer medications target unmistakable stages in both the inherent and extraneous pathways. Proapoptotic atom feeling and antiapoptotic particle restraint are two normal helpful focusing on systems. A portion of the objectives examined incorporate passing receptor ligands, BCL-2 inhibitors, XIAP restraint, and alkylphospholipid analogs (APL) that go about as apoptotic signals. To kill disease cells, by far most of conventional chemotherapeutic specialists depend on BCL-2/BAX-subordinate systems.

Indeed, even through their exemplary avoidance of apoptosis, disease cells can deliver an assortment of signs that quickly lead to apoptosis. Disease cells are 'prepared for death,' and that implies they are almost certain than ordinary cells to start the apoptotic pathway. These prepared cells become more delicate to apoptotic signals. Preparing is brought about by the concurrent expanded articulation of proapoptotic and antiapoptotic proteins, bringing about cells that kick the bucket all the more rapidly and without any problem. On the off chance that the antiapoptotic proteins' upregulation is stopped or disturbed, the proapoptotic protein particles can cause apoptosis. Moving toward prepared cells with a silencer of against - apoptotic proteins might bring about apoptosis and growth cell passing. Moreover, due to natural stressors, disease cells are more helpless to apoptosis.

Moreover, disease cells are more helpless to apoptosis because of natural stressors like low supplement accessibility or hypoxia. Growth cells are altogether more touchy to the extracellular climate than the natural one. The growth silencer p53 advances the record of proapoptotic BCL-2 family proteins. Bcl-2 amily are significant designated spots that direct the fundamental stages of apoptotic cell demise. Another significant protein is p53, too known as growth protein 53, which manages cell cycle or apoptosis and along these lines capacities as a cancer silencer. At the point when there is DNA harm, the p53 protein stops the cell cycle, giving cells time to fix the DNA. At the point when the damage can't be fixed effectively, p53 goes about as a favorable to apoptotic signal. p53 stifles various enemy of apoptotic qualities and additionally could without a doubt actuate apoptotic pathways straightforwardly. Moreover, by restricting to Bcl-XL itself, p53 can dislodge Bax and Bid from prior edifices to Bcl-XL, setting off apoptosis. Apoptosis is a constantly happening, firmly controlled process that holds homeostatic cell balance in a run of the mill creature. Resistant homeostatic instruments can be supported through a typical system, in particular initiation incited cell demise. Clonal development of dynamic resistant cells stifles this cycle. Yolcu et al., 2008 The capacity of Treg cells to multiply and invigorate antigenic reactions is subject to their helplessness to apoptosis, which is influenced by cytokines (Interleukin-2) in the provocative environmental elements. (Yolcu et.al, 2008).

3.3. Correlation between autophagy and apoptosis

As opposed to necrosis, which includes broad cell breaking down and resulting irritation, debased cells are discarded by phagocytosis in both apoptosis and autophagy. As indicated by research, the apoptotic and autophagic processes connect in an intricate manner. In light of the hereditary edge of reference and cell setting of the cells, autophagy may go before or be incited simultaneously with apoptosis. Oligomerized caspase-8 ties to the autophagosome layer, enacting it and laying out a component for the shift from apoptosis to autophagy.

As indicated by the discoveries, invigorated caspase-3 can sever Beclin-1, bringing about a part that moves to mitochondria and actuates apoptosis. Other exploration recommends that the Bcl-2 protein family assists with managing apoptosis as well as cutoff points cell passing brought about via autophagy qualities. Cytotoxic signs can actuate autophagy in apoptosis-safe cells, like those needing to communicate elevated degrees of Bcl-2 or Bcl-xL, lacking Bax and Bak, or presented to container caspase inhibitors like zVAD-fmk, suggesting that autophagy is a default system prompting cell passing. 4 Although embryological fibroblasts from Bax/Bak twofold knockout mice are strong to apoptosis, they can kick the bucket by means of autophagy when animated.

Autophagy inhibitors like 3-MA, bafilomycin, or hydroxylchoroquine, as well as hereditary quieting of autophagic qualities, were utilized to forestall this non-apoptotic cell demise (for instance, ATG5, ATG7, or Beclin-1). This proposes that the autophagic cycle is significant in caspase-free cell demise. Moreover, taking out ATG5 or Beclin-1 in malignant growth cells brought about diminished in cell passing and autophagic influences because of death improvements, without any proof of apoptosis. Various polyphenolic compounds, including curcumin, resveratrol, genistein, and quercetin, initiate autophagy, which prompts cell demise, in malignant growth cells

CHAPTER 4 PLANT COMPOUNDS SHOWING ANTICANCER PROPERTIES

Current disease treatment strategies, like chemotherapy, have downsides because of its hurtful impacts on non-designated tissues, fueling human medical problems. Subsequently, there is a picking various therapies containing normally inferred anticancer specialists, with plants as the favored source. Auxiliary plant metabolites, for example, polyphenols, flavonoids, and brassinosteroids have been researched for their chance use as anticancer specialists. They have been displayed to have anticancer properties like cancer prevention agent action, concealment of disease cell development, enlistment of apoptosis, target explicitness, and malignant growth cell cytotoxicity. Plant-inferred substances have been framed because of positive examination discoveries and are presently being tried in clinical preliminaries. Substances got from vinca alkaloids were among quick to be utilized and are right now being tried in clinical Phase III preliminaries close by Pacitaxel as well as other anticancer specialists. These mixtures are effortlessly gotten from nature and in this manner are commonly non harmful to advance better human cells.

Plant-inferred enemy of - disease specialists are exceptionally sought after in light of the fact that they are intense inhibitor of cancer cell lines. Chemotherapy, for instance, can put the patient under a great deal of pressure and mischief their wellbeing.Thus, there is fundamentally important on utilizing elective disease medicines and treatments. Home grown prescriptions are being utilized and keep on being utilized as the principal wellspring of medication treatment in non-industrial nations for a long time. Plants have been utilized in medication since antiquated times on account of their inborn sterile properties. Subsequently, research has advanced to examine the expected properties. Many plant species have proactively been utilized to treat and forestall malignant growth advancement. Polyphenols, brassinosteroids, and taxols are anticancer mixtures that have been distinguished and separated from earthbound plants. On account of their non-harmful effects on ordinary cells and cytotoxic movement on disease cells, they are popular.. Crude results from organizations could be utilized to recover hostile to - disease drugs from source materials that as of now contain these specialists. Grapes (Vitris vinifera), for instance, are quite possibly the main harvest developed worldwide, and 'grape seed remove' is regularly utilized in food item fixings because of its advantageous wellbeing impacts. Grape stems are an uncooked side-effect of wine creation in the winery business. The winery's expanded natural store can be acidic to the climate. Its high polyphenolic content, then again, may make it useful for anticancer medication advancement or a productive plan to tackle environment influences. Grape stem removes have been displayed to have cell reinforcement properties, to shield DNA from receptive oxygen species, and to have hostile to cancer-causing potential against one assortment of disease cell lines, including cervical malignant growth..

CHAPTER 5 POLYPHENOLS AND THEIR ANTICANCER PROPERTIES

5.1 What are polyphenols

Polyphenols are the most widely recognized bioactive mixtures utilized in business applications because of one's antioxidative, antitumorogenic, antiviral, and antimicrobial properties. Polyphenols can be found in an assortment of plant parts, including organic product, blossoms, leaves, root foundations, stems, and bark. Plant parts gain the qualities of shading, taste, fragrance, astringency, and sharpness because of different metabolites. Polyphenols have two primary capacities in plants: one is to assist with physiological capacities and the other is to go about as a safeguard framework.

Polyphenolic compounds, which additionally incorporate flavonoids, tannins, curcumin, resveratrol, and gallacatechins, are anticancer mixtures. Resveratrol can be seen as in various of food sources, including peanuts, grapes, and red wine. Green tea contains gallacatechins. Polyphenols, which are regular cell reinforcements, are remembered to further develop wellbeing by forestalling of malignant growth. Polyphenols are expected to have apoptosis-actuating and anticancer properties that can be utilized. Polyphenols are expected to start apoptosis by directing the preparation of copper particles that are bound to chromatin, in this manner causing DNA discontinuity.

Resveratrol was shown to be fit for Dna fracture in the contribution of Cu(II). Polyphenols are auxiliary metabolites created by plants in light of different sorts of pressure. Various biotic and abiotic factors, similar to UV, temperature, irritation, microorganisms, etc, cause pressure in plants. These optional metabolites give restorative and medical advantages to plants. The phenol ring is the monomeric part answerable for various sorts of polyphenols. Polyphenols come in around 10,000 unique assortments, each with at least one sweet-smelling rings connected to a hydroxyl bunch. Polyphenols are ordered in view of the quantity of phenolic rings present and the primary components that tight spot to these rings.

They are grouped comprehensively as phenolic acids, flavonoids, stibenes, tannin, and lignan, and these classes are additionally partitioned. Flavonoids represent generally 50% of the absolute number of polyphenols. Curcumin is by a long shot the most dominating normal substance found in many plants among the different curcuminoids. It's being utilized as home grown supplement to treat an assortment of infections. Rottlerin, genistein, quercetin, curcumin, and resveratrol are a couple of instances of mixtures that have been displayed to initiate autophagy demise in malignant growth cells.

5.2 Quercetin

Quercetin's disease battling properties incorporate the inception of cycle capture, apoptosis, and cancer prevention agent capacities. In vivo and in vitro investigations have shown that quercetin initiates apoptosis in disease cells at different phases of the cell cycle without influencing typical cells. Its cancer prevention agent properties shield cells from oxidative pressure, irritation, and DNA harm, and it tweaks the development of numerous disease cell

lines by restraining growth cell multiplication and prompting apoptosis. Besides, quercetin safeguarded against the advancement of liver disease in rodents given a malignant growth inducer. Researchers are progressively keen on examining the relationship of quercetin with exemplary chemotherapeutics. Quercetin has been displayed in both vitro and in vivo investigations to upgrade the adequacy of comparing drugs by expanding their bioavailability and amassing, as well as sharpening disease cells to such malignant growth treatments. One of the most plentiful normally happening polyphenols is the flavonol quercetin (3,3',4',5,7-pentahydroxyflavone). Quercetin can be found in an assortment of plant parts (leaves, grains, and organic products), as well as food sources and drinks like tea and red wine. Quercetin represses cancer development by modifying the presence of apoptosis-subordinate proteins. MCF-7 (human bosom carcinoma cell line) cells treated with quercetin showed portion and time-subordinate brought down multiplication and apoptosis commencement through Bax upregulation and Bcl-2 downregulation.

Hela (cervical malignant growth cell line) cells were demonstrated to be hindered in expansion, prompted autophagy by LC3B-I change into LC3B-II in a fixation subordinate way, and fundamentally advanced apoptosis by quercetin and autophagy inhibitors. The inhibitor chloroquine, as well as siRNA-intervened particular extraction of Atg5 or Beclin-1, improved apoptotic cell demise, inferring that autophagy safeguards against quercetin-incited apoptosis. In epithelial disease cells, quercetin treatment caused broad intracellular vacuolization and phagolysosome development, as well as the gathering of autophagic biomarkers, bringing about cell cycle capture and apoptosis. Quercetin actuates exhaustive autophagy and passing of cells in malignant growth cells by means of proteasomal action and mTOR flagging restraint.

5.3 Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)- 1,6-heptadiene-3,5-dione] is a brilliant yellow hydrophobic polypheno found in the rhizome of Curcuma longa, an enduring spice in the Zingiberaceae family. Curcumin can impact various flagging pathways, including cell multiplication, cell endurance, caspase initiation, passing receptor, mitochondrial, protein kinase, and growth silencer pathways. Curcumin generally affects disease cells and has been demonstrated to be productive and valuable in bosom, lung, prostate, pancreatic, oral, colorectal, myeloma, and head and neck squamous cell carcinoma. Curcumin represses both apoptotic pathways. It can meddle at various places in the flagging fountain. Curcumin restrains BCL-2 and XIAP, prompting expanded articulation of BAX and BAK. Curcumin likewise improves the limit of mitochondria to start mitochondrial layer conductivity [33], bringing about expanded cytochrome discharge, caspase actuation, and apoptosis. Curcumin has been displayed in different malignant growth models to repress cell expansion and angiogenesis, boycott cell cycle movement in cancer cells, and initiate apoptosis. Curcumin was found to fundamentally smother multiplication and initiate cell passing in HT-29 (human colon disease cell line) cells through the mitochondrial cell demise pathway in a new report. Curcumin decreases Bcl-xL/Bad and Bcl-2/Bax proportions, which is incited by caspase-3 actuation. Curcumin hindered development, actuated apoptosis, repressed PI3K/AKT, and delivered cytochrome c, poly (ADP-ribose) polymerase (PARP), and severed caspase-3 in human T-leukemia cell lines. Curcumin additionally hindered cell multiplication, instigated apoptosis, expanded caspase-3 action, upregulated miR192-5p, and smothered PI3K/AKT motioning in A549 cells (human non-little cellular breakdown in the lungs cell line). Curcumin advanced apoptosis-initiated autophagy by expanding the quantity of autophagic vesicles and the outflow

of Atg3, Beclin, and LC3B-II protein. Curcumin sharpens TRAIL-safe LNCaP cells (human prostate disease cell line) in vivo through an assortment of instruments.It initiates passing receptors, upregulates proapoptotic Bax and Bak proteins, smothers antiapoptotic Bcl-xL proteins, and hinders VEGF, MMP-2, and MMP-9 actuation, which are all significant in metastasis, attack, and angiogenesis. These investigations have affirmed that curcumin meaningfully affects an assortment of disease cell lines and that it ought to be considered in malignant growth drug advancement. Curcumin fundamentally focuses on the PI3K/Akt/mTOR flagging pathway as well as NF-B controlled proteins. A few examinations found that curcumin animated G2/M capture and autophagy in harmful glioma cells by restraining the Akt/mTOR/p70S6K and actuating the ERK1/2 pathways, suggesting that autophagy-incited cell passing could be pathway explicit. has been shown not exclusively to prompt apoptosis all alone, yet additionally to have synergic impact with different medications.has been proven to not only induce apoptosis on its own but to also have synergistic effects with various FDA-approved drugs via major inflammatory biomarkers and oncoproteins. As curcumin promotes autophagy similarly via most of these proteins, therefore this compound is effective in inducing both apoptosis and autophagy in cancer therapy.

5.4 Resveratrol

Resveratrol (3,5,4'- trihydroxystilbene), a normally happening polyphenolic compound, is a stilbene found in berries, grapes, peanuts, and other plant sources. Resveratrol is antioxidative, cardioprotective, estrogenic/hostile to estrogenic, mitigating, and antitumor. This substance is likewise very much perceived for its anticancer movement. Resveratrol has been demonstrated to be useful in forestalling all phases of disease advancement, including prostate, bosom, stomach, colon, lung, thyroid, and pancreatic malignant growth cell lines. Different enemy of malignant growth cell strategies for resveratrol have been proposed, including angiogenesis restraint, metastasis hindrance, and apoptosis acceptance. Resveratrol has been displayed to safeguard against various diseases, including bosom, prostate, colorectal, lung, ovarian, cervical, hepatic, and gastric malignant growth. Resveratrol restrains cell development (because of more prominent responsive oxygen species (ROS) levels) and incites apoptosis. Resveratrol therapy actuated mitochondrial-interceded caspase-subordinate apoptosis in prostate disease cells. The G2/M stage cell cycle capture, expanded ROS age, and endoplasmic reticulum (ER) stress prompted apoptosis were completely seen in a human melanoma cell line treated with resveratrol. Resveratrol hinders development and causes demise in MHCC97-H (human hepatocellular disease cell line) cells by initiating autophagy and expanding the declaration of Beclin1, LC3B II/I, and directing the p53 and PI3K/AKT pathways.

Resveratrol invigorates autophagy in B16-F10 cells by upgraded articulation of Beclin1 and LC3B-II/LC3B-I proteins while diminishing the outflow of p62. It additionally prevents the PI3K/AKT/mTOR pathway. Autophagy is for sure a versatile reaction to supplement exhaustion, and resveratrol has been displayed in ovarian malignant growth cells to animate a starvation-like flagging reaction, that is to say, bringing down the phases of phosphorylated Akt and mTOR to start autophagy. Intense resveratrol openness can instigate autophagy, though drawn out openness actuates a caspase-interceded cell demise pathway. In another review, resveratrol improved ROS levels in colon malignant growth cells by prompting caspase-8 and caspase-3 cleavage and expanding LC3-II articulation. SIRT1, one of the most all around considered resveratrol targets, was found to prompt both autophagy and apoptosis when initiated by this compound. Among food-determined polyphenols tried for chemopreventive viability,

resveratrol, a stilbene found in high fixations in grapes, is especially charming because of its capacity to influence a wide cluster of intracellular facilitators associated with malignant growth inception, advancement, and movement. It explicitly restrains cell multiplication and causes apoptosis. The actuated apoptosis by resveratrol has recently been connected to expanded caspase action. Bcl-2 as well as Bcl-XL levels were diminished, while Bax levels were expanded.

5.5 How can they affect autophagy

Quercetin invigorated broad autophagy and ensuing demise all through malignant growth cells by means of proteasomal movement and mTOR flagging hindrance. Curcumin invigorated G2/M capture and autophagy in dangerous glioma cells by repressing the Akt/mTOR/p70S6K and actuating the extracellular sign directed kinase (ERK)1/2 pathways, inferring that autophagy-intervened cell passing could be pathway explicit. Resveratrol instigated cell passing through autophagy in five ovarian disease cell lines, suggesting that treating apoptosis-safe ovarian cancer could be utilized. Intense resveratrol openness instigates autophagy, though long haul openness invigorates a caspase-interceded cell demise ways.

Materials and Methods:

1. Materials:

Database and Servers used: a) National Centre for Biotechnology Information (NCBI)

b) Protein Data Bank (PDB)

c) PubChem

d) PubMed

Softwares Used: a) Discovery Studio Visualizer

b) Open Babel

c) AutoDock

d) Pymol

Selected Autophagy regulators: AMPK, Beclin-1(BCN-1), LC3, ULK1 and ATG7

Selected polyphenolic compounds: Quercetin, Curcumin & Resveratrol

2. **Methods**:

Downloading the above tools

i) **Literature search to find the plant compounds showing anti cancer properties via induction of apoptosis**: The research papers are searched in the database PubMed (https://pubmed.ncbi.nlm.nih.gov/) regarding anti cancer plant compounds and the ones which have been reported to show anti cancer properties through the induction of apoptosis were selected, which included Quercetin, Curcumin and

Resveratrol.

ii) **Downloading the PDB structures of Autophagy regulators(proteins)** :3D structures of proteins AMPK, Beclin-1(BCN-1), LC3, ULK1 and ATG7 are downloaded from the database protein data bank (PDB) in PDB format (https://www.rcsb.org/)

iii) **Downloading the compounds structure from Pubchem:** 3D Structures of the polyphenolic compounds Quercetin, Curcumin and Resveratrol are downloaded from the database PubChem (https://pubchem.ncbi.nlm.nih.gov/) in sdf format. Conversion of sdf file to pdb file: The sdf file of 3D structures are converted to PDB format using Open Bable software

iv) **Protein pre-processing:** The downloaded protein structure is pre processed in "Discovery Studio visualizer 2020" The protein is loaded and the water molecules present in the protein are removed and polar hydrogen atoms are added. The ligand/s attached to the proteins is/are selected and binding site/s is/are defined followed by removing the ligands.

v) **Preparation of protein and ligand** Creation of a work folder followed by setting the directory to workfolder path after running ADT so that all the files get saved in one folder and making it more convenient. Removal of water to make computations easier and clear the binding pocket of possible water molecules that would distort the pose search. Add hydrogens to find hydrogen bond interactions and binding affinity of ligand and protein and kolman charges (template value for each amino acid) to protein and compute gasteiger (on the basis of electronegative equillibration in case there are no partial charges) charges to ligand and save the ligand file as pdbqt(protein data bank, partial charge (q), atom type format(t)). Charges are added because macromolecules are present in the charged form inside human body.

vi) **Execution of AutoGrid4:**Autogrid helps utilities automate distributed energy management. Set the grid BOX according to the x, y, z coordinates of the active site and save the output as gpf. Select program pathname and parameter filename

vii) **Perform docking:**The pre-processed protein molecule and the compounds/ligands to be screened are imported and converted to the ligand pdbqt format. The docking is performed by running Autodock.The output files are analysed to find the top ligands (with low binding affinity energy).

viii) **Analyse the results:**Structure visualization protein-ligand complex: The pre-processed protein molecule and the ligand molecule(best orientation) in its PDB format is loaded in Pymol. The protein and ligand molecule can be set to different forms(like chain, cartoon, stick, surface etc.) and the protein-ligand complex is visualized. The PDB files of both protein and ligand molecule is saved in a single PDB file or can be exported as image.

RESULTS:

The plant compounds to be screened and Autophagy regulators were docked using autodock software. After docking a list of ligands with their binding energy or binding affinity was observed. The more negative the energy is, the better the ligand and strong the binding. The docking result with the highest negative energy were selected. All of the compounds bound to the regulators on side pockets representing the allosteric site of the protein.

Following are the results of docking:

1. **AMPK and Quercetin**

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
targetpymol.pdb	quercetin1.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4892	546.10	-58.08	-2.40 -0.56 0.94 27.59 5.94 177.47	result.1.pdb
2	4850	565.60	-80.62	1.36 0.89 2.85 -4.96 -18.55 200.13	result.2.pdb
3	4848	566.90	-56.74	-0.04 0.09 -0.94 17.84 65.69 174.65	result.3.pdb
4	4622	522.70	-75.29	-2.52 0.90 -0.19 -1.42 15.80 174.18	result.4.pdb
5	4594	517.60	-173.43	2.29 -0.89 -2.69 -60.95 -20.00 165.79	result.5.pdb
6	4552	493.60	-85.46	0.55 -0.69 0.42 -42.97 -41.90 176.09	result.6.pdb
7	4530	532.90	4.79	0.27 -0.17 2.79 0.03 -36.77 209.86	result.7.pdb
8	4506	538.40	-60.99	-2.32 -0.66 0.43 -35.05 -81.44 184.00	result.8.pdb
9	4502	545.60	9.89	-0.92 0.08 2.47 36.73 17.16 165.43	result.9.pdb
10	4492	585.30	-16.20	0.49 -0.84 -1.91 -9.25 -52.20 190.04	result.10.pdb
11	4488	506.80	-49.68	-0.58 0.98 -0.27 -62.68 -3.36 126.62	result.11.pdb
12	4480	515.90	-182.79	-0.87 0.67 2.92 -18.36 -5.18 184.15	result.12.pdb
13	4432	593.90	-76.02	2.38 0.58 1.43 -15.92 -75.54 170.52	result.13.pdb
14	4414	483.20	-147.96	2.93 -1.30 -2.02 -72.19 -7.01 157.58	result.14.pdb
15	4392	510.40	11.41	0.92 0.16 1.95 0.15 4.31 204.21	result.15.pdb
16	4360	522.10	-102.16	-3.02 1.20 -1.32 -72.06 -12.56 129.55	result.16.pdb
17	4332	509.50	-113.98	-2.45 -0.40 -2.96 34.08 55.56 173.19	result.17.pdb
18	4322	560.70	-92.30	3.05 0.14 1.00 -18.08 -89.83 175.13	result.18.pdb
19	4292	585.50	0.24	0.53 -0.52 -0.54 7.70 50.61 197.16	result.19.pdb
20	4286	513.80	-161.80	2.68 0.39 2.51 -0.01 -70.26 177.29	result.20.pdb

show next 20 »»

Table 1: Result of docking between Ampk and Quercetin

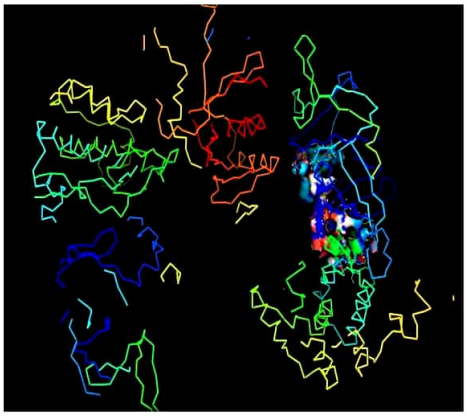

Figure 4: Solid structure Depiction of Ampk bound to Quercetin at side pocket

2. **Ampk and Curcumin**

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
targetpymol.pdb	curcumin.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	6304	760.70	-111.41	-0.92 0.17 1.31 -37.21 -41.27 185.83	result.1.pdb
2	6168	748.50	-132.81	-1.69 -0.13 1.82 40.27 9.04 169.10	result.2.pdb
3	6112	704.90	-85.16	1.12 -0.83 -2.96 -22.17 -56.07 217.78	result.3.pdb
4	5982	827.20	-123.29	-1.99 0.45 2.39 -7.30 -18.61 184.13	result.4.pdb
5	5966	718.70	-162.48	0.97 -0.28 0.65 -43.48 -73.35 198.18	result.5.pdb
6	5938	720.40	-123.75	-0.42 -1.13 -1.30 -16.41 6.08 220.07	result.6.pdb
7	5912	700.80	-173.14	-2.98 -1.09 -1.37 -43.11 1.87 232.96	result.7.pdb
8	5902	697.20	-121.10	1.24 0.88 -0.10 -58.08 -26.12 156.35	result.8.pdb
9	5900	672.40	-153.06	3.08 -1.37 2.23 -46.43 -10.02 168.29	result.9.pdb
10	5886	735.00	-132.54	-1.25 0.52 3.03 5.82 15.03 178.37	result.10.pdb
11	5830	720.90	-114.06	-0.77 0.16 0.32 -41.61 -17.23 188.20	result.11.pdb
12	5796	780.40	-230.19	2.28 1.25 0.38 0.22 36.97 156.83	result.12.pdb
13	5788	741.00	-127.51	-1.30 -1.10 -2.08 48.17 48.56 195.89	result.13.pdb
14	5786	680.90	-96.98	-0.87 -0.82 1.68 -7.65 -4.66 210.49	result.14.pdb
15	5774	715.60	-83.57	-2.83 -0.25 -2.87 -3.19 -1.29 202.48	result.15.pdb
16	5768	821.10	-152.73	0.01 -1.14 0.65 -42.61 -4.77 232.78	result.16.pdb
17	5764	786.10	-8.51	0.05 0.98 1.23 -49.35 -44.85 146.45	result.17.pdb
18	5742	819.00	-89.19	0.05 0.07 0.47 -36.86 -55.70 177.02	result.18.pdb
19	5724	730.20	-105.59	-1.43 0.65 2.74 18.32 18.64 136.58	result.19.pdb
20	5720	667.90	-48.95	1.60 -0.22 -2.52 -27.97 -42.63 173.84	result.20.pdb

show next 20 »»

TABLE 2 Result of docking between Ampk and Curcumin

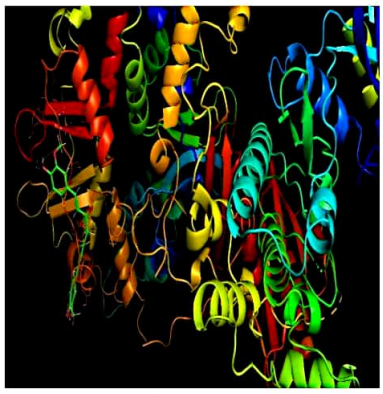

Figure 5 cartoon depiction of ampk docked with Curcumin at the side pockets

3 AMPK and Resveratrol

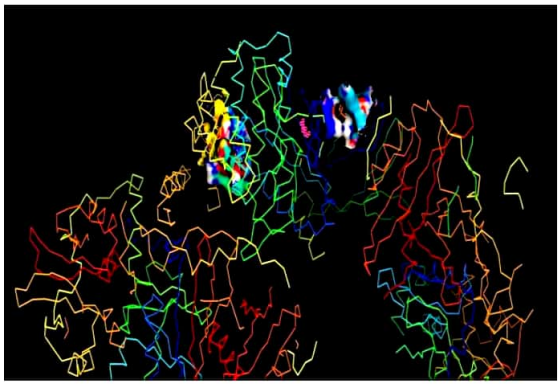

Figure 6 Solid structure depiction of Ampk docked with Resveratrol at side pockets

4 BCN-1 and Quercetin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
beclin1pymol.pdb	quercetin1.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4750	542.00	-56.98	-3.04 -0.22 3.00 13.92 -12.39 7.07	result.1.pdb
2	4612	543.90	-113.55	-0.36 -0.01 -0.75 -9.33 -2.69 1.19	result.2.pdb
3	4376	488.90	-90.18	-2.78 -0.11 2.20 15.15 -30.23 2.94	result.3.pdb
4	4350	559.50	-86.78	-1.92 -0.33 -0.58 -26.62 -15.72 1.06	result.4.pdb
5	4298	526.70	-107.40	2.90 -0.15 -1.04 -23.89 -15.29 10.27	result.5.pdb
6	4218	539.30	-132.30	3.04 0.11 -0.24 -23.23 -31.15 4.35	result.6.pdb
7	4146	516.40	-127.91	-3.11 0.10 1.24 2.41 -41.56 2.95	result.7.pdb
8	4138	523.60	-114.61	-2.14 0.53 2.87 4.94 -16.69 -12.70	result.8.pdb
9	4098	471.80	-1.61	-3.04 0.27 -2.86 5.52 -6.45 -0.31	result.9.pdb
10	4094	518.70	-145.04	-2.84 -0.08 -0.22 -25.87 -28.32 1.56	result.10.pdb
11	4046	541.10	-98.65	-0.82 -0.80 -2.93 17.01 -29.06 13.28	result.11.pdb
12	4018	476.30	-80.89	-3.13 -0.07 -2.26 -3.74 -2.03 5.23	result.12.pdb
13	4012	529.80	-163.54	2.63 0.28 0.58 -13.66 -43.98 5.13	result.13.pdb
14	4010	488.60	-70.42	-0.21 0.21 3.11 7.60 -33.73 -2.11	result.14.pdb
15	3938	487.10	-128.95	-0.98 0.14 0.31 -20.39 -21.27 -8.19	result.15.pdb
16	3864	537.00	-73.33	1.91 -0.89 -3.08 -5.04 -19.92 26.08	result.16.pdb
17	3848	532.20	-176.47	-2.34 -0.56 -2.58 11.09 -5.96 7.49	result.17.pdb
18	3826	509.10	-122.12	2.80 0.48 -0.54 -21.25 -25.95 1.82	result.18.pdb
19	3804	463.30	-55.18	-0.31 0.51 2.88 3.49 -38.49 -4.70	result.19.pdb
20	3788	420.60	-47.01	-0.40 0.38 -1.62 7.77 -10.18 -4.77	result.20.pdb

show next 20 »»

Table 3 result of docking between BCN-1 and Quercetin

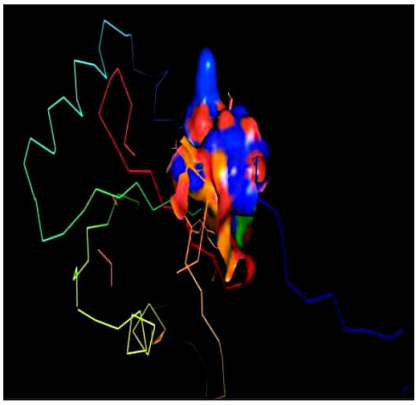

Figure 7 Solid structure depiction of BCN-1 bound to quercetin at the side pockets

5. BCN-1 and Curcumin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
beclin1pymol.pdb	curcumin.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	6164	792.20	-170.73	2.60 -0.18 -0.32 -23.78 -26.50 19.40	result.1.pdb
2	5744	744.70	-214.68	-0.54 -0.23 -0.54 -23.88 3.30 5.06	result.2.pdb
3	5710	714.80	-135.36	3.11 -0.04 -2.26 1.54 10.84 5.94	result.3.pdb
4	5336	772.60	-111.51	3.11 -0.19 2.71 25.54 -20.99 9.68	result.4.pdb
5	5290	770.60	-208.40	2.55 0.39 -1.46 -10.85 6.46 4.46	result.5.pdb
6	5278	627.20	-67.13	0.44 -0.10 2.52 10.63 -50.55 14.50	result.6.pdb
7	5256	773.10	-100.41	2.88 -0.16 0.01 -19.86 -37.64 14.72	result.7.pdb
8	5222	664.80	-75.38	-2.99 -0.20 -0.29 -18.75 -35.08 9.77	result.8.pdb
9	5152	653.10	-131.01	0.61 0.61 -2.02 43.35 -9.86 -14.76	result.9.pdb
10	5148	708.30	-184.63	-1.43 1.19 -0.47 6.16 -30.18 -33.47	result.10.pdb
11	5144	732.90	-133.11	0.51 0.10 2.92 17.21 -38.86 12.84	result.11.pdb
12	5094	670.00	-211.02	3.12 0.20 -1.93 -9.45 7.99 0.70	result.12.pdb
13	5094	644.80	-128.89	3.14 -0.13 -0.45 -38.30 -22.80 8.01	result.13.pdb
14	5052	682.00	-127.33	-0.04 0.03 2.40 3.94 -53.07 2.38	result.14.pdb
15	5044	676.60	-207.29	2.75 0.59 -1.46 -20.49 3.47 -5.22	result.15.pdb
16	5018	680.60	-74.08	1.80 -1.09 -2.90 0.06 -26.48 29.10	result.16.pdb
17	4998	682.70	-198.39	2.01 -1.02 1.30 -0.41 -15.91 25.47	result.17.pdb
18	4978	709.00	-109.92	1.70 -0.30 -0.46 -18.44 -21.93 20.72	result.18.pdb
19	4922	594.70	-90.66	2.83 -0.20 2.70 29.23 -20.06 14.94	result.19.pdb
20	4906	591.50	-148.73	-1.30 0.68 2.32 17.43 -16.12 -36.94	result.20.pdb

show next 20 »»

Table 4 Result of docking between BCN-1 and Curcumin

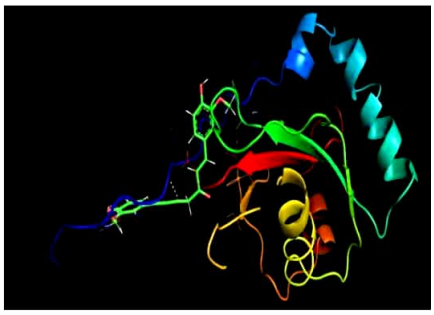

Figure 8 cartoon depiction of BCN-1 bound to curcumin at side pockets

6. BCN-1 and Resveratrol

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
beclin1pymol.pdb	resveratrol.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	3822	473.70	-106.72	-3.03 0.06 -0.97 -23.61 -15.40 2.74	result.1.pdb
2	3808	481.70	-101.85	2.93 0.42 2.83 10.09 -14.29 1.12	result.2.pdb
3	3704	504.70	-122.55	3.12 0.48 -2.91 14.49 -7.79 0.15	result.3.pdb
4	3608	439.00	-116.98	0.87 -0.14 2.48 1.84 -34.84 15.94	result.4.pdb
5	3548	424.40	-78.61	3.08 0.02 1.80 7.98 -35.80 5.32	result.5.pdb
6	3508	426.60	-76.82	-2.45 0.10 -1.93 -8.88 -0.53 -3.16	result.6.pdb
7	3480	454.10	-45.77	2.97 0.27 -1.60 -3.78 -8.17 3.64	result.7.pdb
8	3456	478.00	-132.28	-3.00 0.31 -0.53 -20.44 -25.59 -1.72	result.8.pdb
9	3428	429.50	-109.28	-1.82 -1.32 -0.24 -13.71 -28.93 14.10	result.9.pdb
10	3408	373.90	-159.05	-1.33 0.32 0.35 -21.91 -15.54 -22.67	result.10.pdb
11	3406	409.40	-79.58	-1.64 0.06 2.31 31.18 -22.48 -14.30	result.11.pdb
12	3404	445.30	-93.00	-0.55 0.08 1.02 -22.26 -27.47 -1.32	result.12.pdb
13	3402	409.40	-36.98	-3.13 -0.09 -2.58 1.11 -4.92 5.20	result.13.pdb
14	3400	416.70	-73.10	-1.70 -1.27 -0.15 -13.19 -30.05 8.24	result.14.pdb
15	3394	423.10	-105.10	1.73 -0.24 -0.74 7.15 -2.40 12.49	result.15.pdb
16	3358	425.60	-118.21	0.28 -0.25 -0.63 -13.25 -1.56 11.59	result.16.pdb
17	3348	449.40	-105.92	-2.66 0.69 -0.90 -19.21 -18.30 -7.06	result.17.pdb
18	3342	420.20	-41.12	2.70 -0.03 -0.87 -9.29 -18.14 11.19	result.18.pdb
19	3336	444.00	-97.69	1.83 1.20 2.89 18.57 -31.45 -14.06	result.19.pdb
20	3334	481.10	-138.16	3.07 0.32 2.79 22.83 -14.77 1.66	result.20.pdb

show next 20 »»

Table 5 Result of docking between BCN-1 and Resveratrol

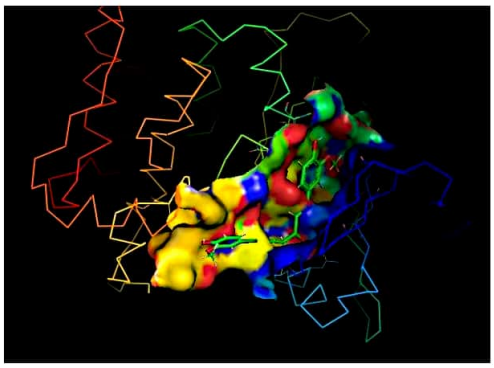

Figure 9 solid structure depiction of BCN-1 bound to Resveratrol at side pockets

7. ULK1 and Quercetin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
ulk1pymol.pdb	quercetin1.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4556	514.90	-134.48	0.18 -0.90 -1.21 1.36 -22.75 5.83	result.1.pdb
2	4216	491.00	-73.30	2.00 0.07 -2.17 5.91 -24.06 8.87	result.2.pdb
3	4116	508.60	-85.28	-2.12 -1.13 -2.29 5.81 -35.97 -4.08	result.3.pdb
4	4104	503.60	-105.69	-0.03 1.09 2.40 -9.58 -52.92 -28.47	result.4.pdb
5	4066	477.60	-65.63	-2.29 -0.46 0.57 -17.72 -55.39 -15.35	result.5.pdb
6	3958	472.10	-66.14	1.29 -1.06 -2.77 1.48 -55.95 9.21	result.6.pdb
7	3954	499.00	-38.82	-2.55 -0.11 1.19 1.72 -64.45 -5.54	result.7.pdb
8	3928	467.40	-51.01	0.66 0.86 -1.76 14.22 -37.47 -20.62	result.8.pdb
9	3888	447.40	-147.50	1.27 -0.38 -0.67 -16.37 1.67 -2.20	result.9.pdb
10	3876	424.00	-13.32	1.07 1.37 -1.11 -0.58 -37.26 -31.05	result.10.pdb
11	3836	494.00	-88.27	-0.91 0.73 -2.50 7.25 -44.98 -17.72	result.11.pdb
12	3832	454.20	-152.45	-2.23 0.40 3.00 10.82 -34.67 -33.17	result.12.pdb
13	3822	456.10	-25.21	-0.65 -0.78 1.72 -5.59 -70.57 -5.39	result.13.pdb
14	3822	532.80	-111.52	3.09 0.63 -2.84 9.32 -28.43 -11.69	result.14.pdb
15	3816	437.00	-27.96	-2.31 0.60 1.43 7.79 -49.88 -16.87	result.15.pdb
16	3800	450.90	-77.22	-1.09 1.20 1.94 -10.23 -13.54 -46.08	result.16.pdb
17	3792	439.00	-25.31	-1.26 0.12 -0.27 -25.72 -38.49 -37.32	result.17.pdb
18	3756	462.70	-150.79	-2.89 -0.90 0.31 -13.54 -53.75 -5.67	result.18.pdb
19	3750	501.10	-111.38	-2.47 -0.97 0.19 -15.94 -54.93 11.30	result.19.pdb
20	3714	453.20	-91.82	1.22 -0.21 -0.64 -15.42 1.72 -3.35	result.20.pdb

show next 20 »»

Table 6 Result of docking between ULK1 and Quercetin

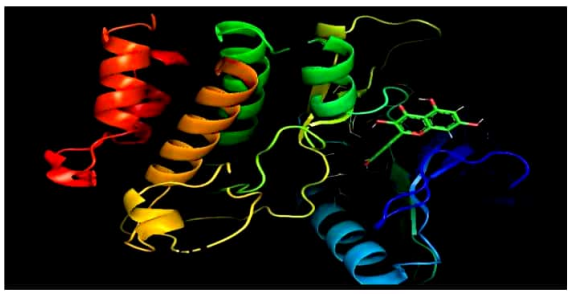

Figure 10 Cartoon structure of ULK1 docked with Quercetin and side pockets

8. ULK1 and Curcumin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
ulk1pymol.pdb	curcumin.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	5686	669.00	-35.35	1.26 0.46 3.00 18.81 -55.17 -23.22	result.1.pdb
2	5546	685.40	-147.30	-1.42 0.57 2.35 3.41 -24.86 -48.56	result.2.pdb
3	5534	794.90	-166.13	-2.31 0.36 1.73 8.24 -60.10 -36.46	result.3.pdb
4	5460	640.50	-141.37	-0.54 0.71 2.49 -3.17 -55.71 -32.57	result.4.pdb
5	5444	719.10	-213.98	2.22 -0.55 -1.32 -21.47 -22.50 12.43	result.5.pdb
6	5428	654.30	-77.11	-1.10 -0.42 -0.02 -40.12 -39.83 -24.46	result.6.pdb
7	5380	642.20	-193.88	1.26 0.16 -0.58 -27.47 6.71 -12.44	result.7.pdb
8	5344	687.10	-172.13	-2.07 -0.84 -1.09 -26.22 10.24 -8.48	result.8.pdb
9	5298	641.70	-71.65	-1.00 1.17 0.73 -3.61 -46.84 -41.44	result.9.pdb
10	5268	613.90	-117.75	0.42 -0.35 -0.50 -22.72 -9.17 8.79	result.10.pdb
11	5266	722.10	-191.29	1.50 -0.98 -1.05 -5.71 -9.95 8.25	result.11.pdb
12	5230	708.70	-102.83	3.13 1.09 -3.12 7.26 -1.93 -36.74	result.12.pdb
13	5222	731.70	-207.84	2.83 -1.33 -0.34 -9.48 -52.52 -0.80	result.13.pdb
14	5216	708.60	-120.76	0.62 0.20 1.56 -11.52 -69.82 1.44	result.14.pdb
15	5212	688.20	-74.68	1.21 -0.79 -1.62 7.04 -44.15 18.63	result.15.pdb
16	5210	678.60	-132.19	-2.74 0.80 2.41 10.78 -32.54 -32.20	result.16.pdb
17	5194	631.00	-145.54	2.02 0.75 2.27 15.72 -28.51 -28.62	result.17.pdb
18	5192	678.40	-65.52	0.02 1.01 -0.66 -1.03 -30.33 -36.10	result.18.pdb
19	5180	695.50	-79.56	0.98 -1.04 -2.23 8.63 -54.72 15.07	result.19.pdb
20	5176	648.40	-160.21	-1.32 0.37 2.40 3.43 -25.98 -44.34	result.20.pdb

show next 20 »»

Table 7 Result of docking between ULK1 and Curcumin

Figure 11 Cartoon depiction of ULK1 bound to curcumin at side pockets

9. ULK1 and Resveratrol

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
ulk1pymol.pdb	resveratrol.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	3890	466.30	-113.27	-0.08 -0.92 -1.58 3.15 -26.15 2.45	result.1.pdb
2	3878	436.20	-89.33	1.52 -0.18 -0.65 -16.38 -2.84 -6.91	result.2.pdb
3	3830	446.50	-37.52	1.69 -0.09 -1.99 4.47 -27.36 12.72	result.3.pdb
4	3800	453.10	-97.36	-2.49 -0.32 0.84 -6.33 -62.46 -2.81	result.4.pdb
5	3792	450.20	-114.15	-0.24 0.89 1.94 -14.33 -48.52 -24.85	result.5.pdb
6	3714	467.10	-118.25	-0.97 -1.04 1.48 -7.21 -69.61 0.83	result.6.pdb
7	3626	462.70	-97.49	2.29 -0.05 -0.81 -15.91 -37.53 -21.99	result.7.pdb
8	3624	432.90	-32.33	1.06 0.96 -1.55 6.29 -35.45 -20.46	result.8.pdb
9	3614	427.30	-55.78	-0.40 -1.22 2.44 1.18 -66.77 -0.02	result.9.pdb
10	3592	425.00	-139.64	-1.27 0.09 2.47 2.23 -22.38 -32.21	result.10.pdb
11	3582	488.30	-174.84	-2.50 0.79 2.98 2.85 -32.69 -33.16	result.11.pdb
12	3558	432.10	-97.24	-1.24 0.45 2.39 -0.10 -22.07 -37.82	result.12.pdb
13	3544	432.20	-76.43	-2.27 0.65 1.29 4.73 -49.48 -16.08	result.13.pdb
14	3542	447.60	-139.07	-0.93 -0.46 -2.50 13.89 -31.52 -11.58	result.14.pdb
15	3506	433.40	-110.56	-0.51 -0.76 -0.53 -13.49 -22.77 -8.24	result.15.pdb
16	3504	418.50	-124.02	0.84 0.05 1.75 -34.95 -42.44 -5.31	result.16.pdb
17	3494	407.00	-165.23	1.58 -0.42 -0.72 -17.17 -2.79 -3.89	result.17.pdb
18	3484	400.40	-48.45	-1.26 0.52 -1.30 -29.86 -12.76 -33.53	result.18.pdb
19	3478	444.60	-52.71	-2.32 -0.73 -2.95 -12.68 -1.77 -8.85	result.19.pdb
20	3460	483.00	-148.86	-0.15 0.58 -3.14 -20.29 -38.06 -21.96	result.20.pdb

show next 20 »»

Table 8 Result of docking between ULK1 and Resveratrol

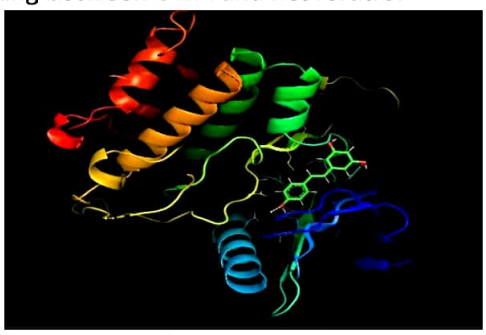

Figure 12 Cartoon depiction of ULK1 bound to Resveratrol at side pockets

10. ATG7 and Quercetin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
atg7.pdb	quercetin1.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4580	515.00	-100.70	0.45 1.41 1.60 14.48 -9.05 -41.55	result.1.pdb
2	4452	570.10	-213.84	2.62 0.17 0.10 14.19 -8.24 -13.33	result.2.pdb
3	4328	539.00	-132.66	-0.67 0.60 -1.94 9.29 -0.55 -13.55	result.3.pdb
4	4252	490.00	-19.72	0.94 0.58 -0.14 8.73 9.53 -20.89	result.4.pdb
5	4208	476.10	-56.75	0.15 -1.14 -2.41 38.69 -6.33 -4.23	result.5.pdb
6	4144	498.20	-26.78	0.95 -0.62 1.09 -13.29 -10.07 19.43	result.6.pdb
7	4094	498.60	-105.67	1.84 -0.96 -0.21 3.07 -3.91 32.19	result.7.pdb
8	4092	567.30	-155.39	0.28 -0.26 2.03 25.55 -16.37 -9.87	result.8.pdb
9	4080	500.70	-37.80	-1.40 0.15 -1.52 -2.14 19.87 -15.57	result.9.pdb
10	4056	469.50	-64.43	1.53 0.35 -1.58 -3.02 26.45 4.73	result.10.pdb
11	4036	479.70	-155.21	2.30 -0.05 -0.96 13.03 12.19 -8.61	result.11.pdb
12	3976	481.60	-149.40	-2.34 -1.53 -0.57 12.37 -2.38 -9.11	result.12.pdb
13	3946	481.50	-81.55	1.53 -0.57 -3.00 35.60 0.56 -1.82	result.13.pdb
14	3946	501.10	-168.69	2.09 0.60 -2.83 50.11 14.63 -10.27	result.14.pdb
15	3940	526.80	-147.75	-0.18 0.57 -0.78 29.67 20.48 -26.90	result.15.pdb
16	3936	514.10	-91.71	-0.80 1.13 0.70 18.89 4.72 -45.74	result.16.pdb
17	3936	537.30	-159.32	2.25 0.06 1.28 29.04 -17.25 -9.61	result.17.pdb
18	3936	491.70	-184.27	-0.76 -1.16 -1.96 38.52 9.55 -16.21	result.18.pdb
19	3912	525.90	-121.29	-3.10 -0.97 -2.12 21.41 17.03 -4.40	result.19.pdb
20	3912	484.70	-193.74	2.57 1.32 2.71 38.74 2.63 -46.48	result.20.pdb

show next 20 »»

Table 9 Result of docking between ATG7 and Quercetin

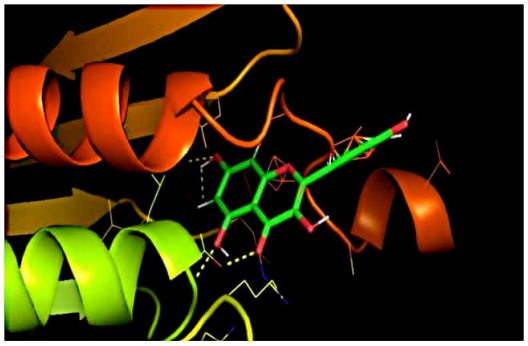

Figure 13 Cartoon depiction of the side pocket of ATG7 bound to Quercetin

11. ATG7 and Curcumin

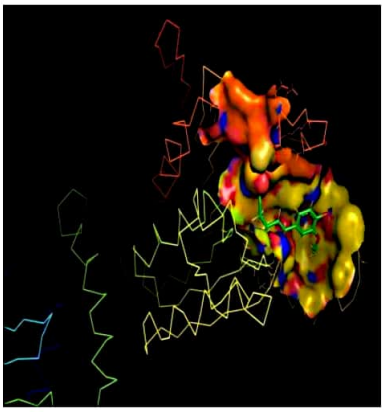

Figure 14 solid structure depiction of ATG7 and Curcumin docking

12. ATG7 and Resveratrol

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
atg7.pdb	resveratrol.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4114	477.90	-81.84	-1.14 0.86 0.39 22.07 3.32 -41.78	result.1.pdb
2	4066	467.70	-190.81	-0.77 -0.47 1.39 16.14 -10.07 -18.08	result.2.pdb
3	4050	525.80	-182.04	-0.30 0.89 -0.23 23.61 15.03 -29.28	result.3.pdb
4	4046	467.50	-37.35	-1.55 1.37 2.16 1.51 0.40 -42.81	result.4.pdb
5	4044	442.60	-49.12	-0.45 0.20 2.13 29.44 -19.88 -26.04	result.5.pdb
6	3992	473.20	-71.06	0.92 -0.96 -2.87 30.42 -6.07 -2.60	result.6.pdb
7	3984	437.00	-52.33	0.48 -0.27 -1.04 30.66 17.04 -8.67	result.7.pdb
8	3958	448.60	-133.01	2.32 1.35 2.64 39.10 -0.40 -45.00	result.8.pdb
9	3894	518.70	-247.12	-0.75 -0.02 -0.11 15.59 14.31 -25.09	result.9.pdb
10	3830	477.40	-57.56	-0.35 0.87 0.87 15.62 1.77 -32.18	result.10.pdb
11	3796	426.50	-97.61	1.04 -0.85 1.02 -10.87 -9.38 21.59	result.11.pdb
12	3786	456.20	-57.67	-1.88 -1.38 -1.12 -3.12 5.39 -8.80	result.12.pdb
13	3768	461.90	-167.13	2.40 -1.49 -1.48 16.47 -8.43 -12.23	result.13.pdb
14	3734	436.10	-91.92	-0.79 0.89 -2.11 5.28 -7.67 -15.63	result.14.pdb
15	3718	489.70	-76.44	1.05 -0.34 1.43 -10.33 -17.85 16.83	result.15.pdb
16	3714	450.70	-107.36	2.23 -0.62 -0.31 -7.10 -4.19 27.87	result.16.pdb
17	3694	419.90	-87.95	-1.97 0.09 0.12 13.78 -5.89 -38.86	result.17.pdb
18	3662	446.40	-66.80	0.69 -1.29 -2.23 30.85 -8.73 -6.44	result.18.pdb
19	3654	435.50	-3.27	-1.10 -0.46 -2.35 24.11 28.55 -35.03	result.19.pdb
20	3628	478.90	-143.53	2.03 0.76 -1.53 22.24 26.09 -24.14	result.20.pdb

show next 20 >>

Table 10 Result of docking between ATG7 and Resveratrol

Figure 15 cartoon depiction of ATG7 bound to Resveratrol at side pockets

13. LC3 and Quercetin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constraints
lc3pymol.pdb	quercetin1.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	4176	482.60	-130.57	0.35 0.12 2.68 -23.02 -4.09 13.81	result.1.pdb
2	4054	516.70	-98.79	-0.01 0.08 1.97 -41.43 -5.28 10.53	result.2.pdb
3	3914	557.60	-165.19	0.52 0.28 1.41 -52.55 3.78 13.65	result.3.pdb
4	3830	512.10	-103.20	2.80 0.04 0.87 -44.22 -2.12 14.67	result.4.pdb
5	3762	539.80	-170.30	-1.71 -0.16 -1.75 -36.82 43.08 3.23	result.5.pdb
6	3710	447.70	-108.41	-2.52 -0.07 2.61 -11.32 14.12 4.91	result.6.pdb
7	3680	482.60	-102.45	2.07 0.35 -1.86 -37.33 46.61 14.77	result.7.pdb
8	3680	442.70	-111.60	1.23 -0.52 0.66 -49.09 26.46 40.75	result.8.pdb
9	3678	464.80	-107.66	-0.45 -0.10 2.95 -27.26 6.02 8.35	result.9.pdb
10	3650	491.50	-69.80	2.19 1.06 -0.18 -53.87 27.60 8.14	result.10.pdb
11	3646	447.20	-83.02	-2.13 0.57 -2.28 -35.68 42.89 0.80	result.11.pdb
12	3642	474.50	-105.75	1.38 0.10 -1.64 -17.02 40.94 9.26	result.12.pdb
13	3630	422.20	-125.00	0.86 -0.43 -2.26 -4.25 29.96 17.92	result.13.pdb
14	3612	424.60	-105.48	-2.13 -0.03 -1.76 -22.27 41.31 -7.69	result.14.pdb
15	3586	407.90	-92.28	-0.40 -0.15 -1.02 -40.57 44.16 10.89	result.15.pdb
16	3562	421.90	-88.74	-1.75 0.17 0.07 -57.04 10.87 -4.71	result.16.pdb
17	3554	470.20	-98.85	1.51 -1.18 0.35 -32.69 32.91 39.42	result.17.pdb
18	3550	487.10	-82.03	-0.55 1.20 -1.85 -34.90 13.02 -7.28	result.18.pdb
19	3522	423.20	-39.33	2.24 0.31 0.18 -55.90 20.11 21.89	result.19.pdb
20	3508	464.80	-73.32	0.40 -0.32 -0.40 -49.51 35.70 22.43	result.20.pdb

show next 20 »»

Table 11 Result of docking between LC3 and Quercetin

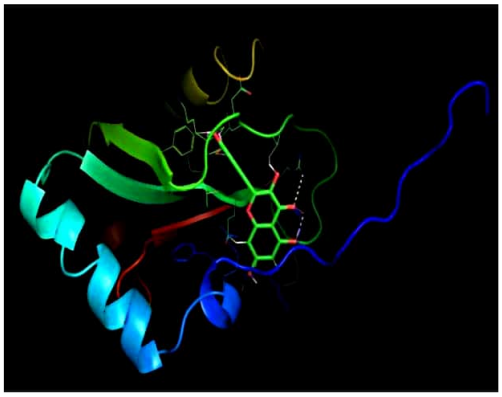

Figure 16 Cartoon depiction of LC3 bound to Quercetin at side pockets

14. LC3 and Curcumin

Receptor	Ligand	Complex Type	Clustering RMSD	User e-mail	Receptor Site	Ligand Site	Distance Constrain
lc3pymol.pdb	curcumin.pdb	Default	4.0	pooja_2k20mscbio20@dtu.ac.in	-	-	-

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	6376	789.20	-184.82	-1.20 -0.24 -0.50 -68.61 34.61 2.97	result.1.pdb
2	6018	734.20	-158.63	0.30 0.29 -0.48 -55.23 41.56 8.40	result.2.pdb
3	5762	721.40	-212.09	-0.33 0.04 -0.14 -60.80 33.10 6.45	result.3.pdb
4	5368	712.40	-164.94	-2.86 0.10 -1.46 -53.51 39.09 5.49	result.4.pdb
5	5298	637.70	-79.46	0.75 -1.39 2.24 -55.65 11.08 40.46	result.5.pdb
6	5294	639.20	-93.74	0.96 1.53 1.94 -48.82 2.60 -7.11	result.6.pdb
7	5260	662.50	-197.98	-2.75 0.44 2.87 -30.94 25.81 0.61	result.7.pdb
8	5192	630.60	-106.09	2.57 1.49 2.94 -26.13 39.59 -4.47	result.8.pdb
9	5174	647.50	-171.72	0.18 0.32 -0.45 -52.30 35.73 6.68	result.9.pdb
10	5130	620.20	-96.31	1.02 -1.17 0.38 -36.97 38.06 39.55	result.10.pdb
11	5114	634.50	-131.56	0.78 0.39 2.79 -31.68 -2.09 16.65	result.11.pdb
12	5040	755.30	-130.02	-0.92 -0.62 0.22 -65.25 17.78 17.59	result.12.pdb
13	5034	654.90	-183.91	-3.09 -0.11 2.86 -20.11 26.48 12.27	result.13.pdb
14	5004	638.20	-194.13	-1.82 -0.62 -0.24 -75.39 17.93 12.55	result.14.pdb
15	4996	619.10	-58.55	0.01 0.44 2.43 -29.44 -7.05 1.35	result.15.pdb
16	4994	600.30	-26.33	1.28 -1.10 0.00 -29.92 36.01 31.94	result.16.pdb
17	4976	666.60	-73.06	-0.93 -1.25 0.14 -61.64 19.85 31.44	result.17.pdb
18	4942	597.60	-54.73	-1.55 -0.16 0.58 -61.49 11.81 -6.45	result.18.pdb
19	4900	643.60	-105.47	2.05 -0.09 -0.01 -49.83 23.62 42.16	result.19.pdb
20	4890	584.60	-58.39	0.74 0.93 -3.03 -4.25 5.89 -6.60	result.20.pdb

show next 20 »»

Table 12 Result of docking between LC3 and Curcumin

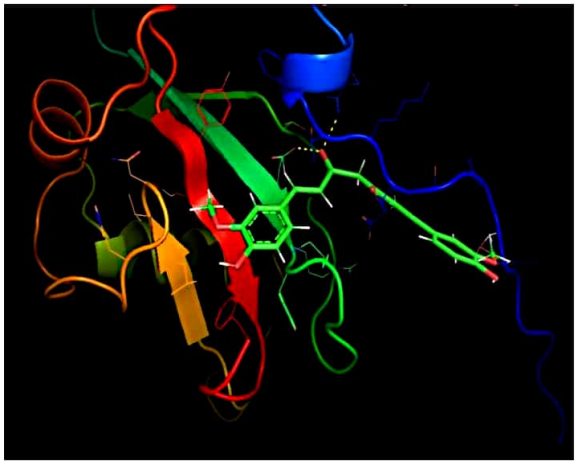

Figure 17 Cartoon depiction of LC3 bound to curcumin at side pocket

15. LC3 and Resveratrol

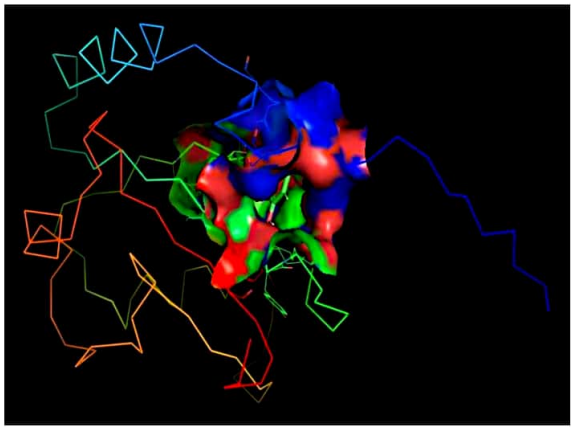

Figure 18 solid structure depiction of LC3 bound to resveratrol at side pockets

CONCLUSION:

Dietary polyphenols have aroused the curiosity of analysts because of their supposed ability to go about as incredibly viable chemopreventive and chemotherapeutic specialists. Truth be told, they can influence the general course of tumorigenesis by smothering favorable to oxidant protein overexpression, repressing explicit qualities engaged with cell cycle, and inciting apoptosis. Expanded growth protection from therapy, whether chemotherapy, radiation therapy, or any of the restorative targets, is one of the most genuine irritating issues in disease treatment. This high opposition is an immediate result of apoptosis surrenders. Autophagy, a sort of elective cell passing, might be the incomparable answer for this issue. Various phytochemical polyphenolic intensifies found in numerous food sources can intercede both accepted and non-authoritative autophagy through utilization of different pathways that target significant proteins in an assortment of malignant growth types. These polyphenols have the ability to invigorate both apoptosis and autophagy, bringing about malignant growth cell passing. Besides, since they are food substances, they might give more prominent security, both as a result of their inborn lower harmfulness and in light of the fact that they take into account lower dosages as well as incidental effects when contrasted with engineered drugs. Attempting to join FDA-endorsed drugs with renowned polyphenolic intensifies like quercetin, curcumin, and resveratrol give a few novel treatments in malignant growth therapy, resolving the huge issue of medication resistance in disease treatment.(N Hasima, 2014) Normal polyphenolic mixtures can cause type II PCD through both accepted (Beclin-1 ward) and non-authoritative (Beclin-1 free) autophagy pathways. Thus, can alter the impacts of flagging pathways and cause cell demise through apoptosis as well as through autophagy. Subsequently, these substances could be utilized related to standard malignant growth treatments. From that point forward, there have been various investigations showing that polyphenolic mixtures, for example, quercetin, curcumin, and resveratrol incite apoptosis in malignant growth cells and can likewise impact autophagy. Following docking, it was found that these mixtures tie to the coat pockets of Autophagy controllers, which is an allosteric site, and subsequently can change the state of the dynamic site and improve substrate restricting, accordingly upgrading the Autophagy cycle. So we can say, these compounds provide anti cancer properties via modulating Autophagy and apoptosis and can be used in anti cancer therapy. Specially in those where cancer cell becomes resistant to apoptosis.

FUTURE PERSPECTIVE:

The longing for new viable disease battling drugs keeps on being a test in clinical science. Regular life forms (e.g., plants, microscopic organisms, and parasites) produce dynamic atoms that can possibly be utilized in medication to treat an assortment of sicknesses, including malignant growth. Polyphenols' wellbeing not entirely settled by both their admission and bioavailability. The ongoing survey gives an outline of some pointed polyphenols (quercetin, curcumin, resveratrol, and kaempferol) and their anticancer impacts in different malignant growth cell lines. Adjustment of sub-atomic systems and flagging pathways associated with cell endurance, augmentation, metastasis, apoptosis, and angiogenesis was the essential method of

activity. Accordingly, future exploration ought to expand the extent of normal mixtures as great wellbeing, protected, productive, and savvy malignant growth therapeutics. The capacity of these compounds to provide a means of cancer cell death that enhances the effects of standard therapies should be taken into consideration for designing novel therapeutic strategies. Thus, these compounds could be used as a co- therapy with standard therapies in cancer.

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CANDIDATE'S DECLARATION

I Pooja, Roll Number: 2K20/MSCBIO/20, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled — **EFFECT OF POLYPHENOLIC COMPOUNDS ON AUTOPHAGY REGULATORS** in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is an authentic record of my own carried out during the period from January- May 2022, under the supervision of Dr. Asmita Das.

Pooja

Date: 6th May 2022

Pooja

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Finally, my thanks go to all the people who have supported me to complete the research work directly or indirectly.

Pooja

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To the best of my knowledge, the above work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere. I further certify that the publication and indexing information given by the student is correct.

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Dr. Asmita Das

Supervisor

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