Natural compounds in the regulation of proteostatic pathways: An invincible artillery against stress, ageing, and diseases

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Abstract Cells have different sets of molecules for performing an array of physiological functions. Nucleic acids have stored and carried the information throughout evolution, whereas proteins have been attributed to performing most of the cellular functions. To perform these functions, proteins need to have a unique conformation and a definite lifespan. These attributes are achieved by a highly coordinated protein quality control (PQC) system comprising chaperones to fold the proteins in a proper three-dimensional structure, ubiquitin-proteasome system for selective degradation of proteins, and autophagy for bulk clearance of cell debris. Many kinds of stresses and perturbations may lead to the weakening of these protective cellular machinery, leading to the unfolding and aggregation of cellular proteins and the occurrence of numerous pathological conditions. However, modulating the expression and functional efficiency of molecular chaperones, E3 ubiquitin ligases, and autophagic proteins may diminish cellular proteotoxic load and mitigate various pathological effects. Natural medicine and small molecule-based therapies have been well-documented for their effectiveness in modulating these pathways and reestablishing the lost proteostasis inside the cells to combat disease conditions. The present article summarizes various similar reports and highlights the importance of the molecules obtained from natural sources in disease therapeutics.

Abbreviations: 17-AAG, 17-allylamino-geldanamycin; APC, anaphase-promoting complex; BAG, BCL2-associated athanogene; CAP, chaperone-assisted proteasomal degradation; CASA, chaperone-assisted selective autophagy; CMA, chaperone-mediated autophagy; CHIP, carboxy-terminus of HSC70 interacting protein; DUBs, deubiquitinases; EGCG, epigallocatechin-3-gallate; ESCRT, endosomal sorting complexes required for transport; HECT, homologous to the E6-AP carboxyl terminus; HSC70, heat shock cognate 70; HSF1, heat shock factor 1; HSP, heat shock protein; KFERQ, lysine-phenylalanine-glutamate-arginine-glutamine; LAMP2a, lysosome-associated membrane protein 2a; LC3, light chain 3; NBR1, next to BRCA1 gene 1; PQC, protein quality control; RING, really interesting new gene; Ub, ubiquitin; UPS, ubiquitin–proteasome system.

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1. Introduction

A eukaryotic cell represents a well-evolved architecture, made up of many small components working independently and coherently. A highly efficient and coordinated way of functioning of multiple subsystems towards the fitness and survival of individual cells and the organism is a highly complex biological phenomenon. It remains a great challenge to understand the intricacies and complexities of the living systems. For a very long period, the central dogma, i.e., the idea of sequential flow of information from DNA to RNA, followed by its retrieval into the form of proteins, remained a mystery for the scientists. However, the improvements in the techniques and adaptations of the newer approaches to decipher the molecular arrangements have led to a higher understanding of the fine details of the cells’ structure and functional arrangements. The involvement of biochemical and molecular biology approaches has led to the deduction of most of the metabolic pathways and their subsequent impact on the cellular physiology. At the same time, structural and computational biologists have played a critical role in providing crucial insights about the mysteries of the genetic codes, amino acid sequences, and structural plans of the proteins. Many other tools have also helped in devising various ways of visualizing and interpreting the intermolecular interactions involved in different cellular pathways and mechanisms.

With all the advancements and our current understanding of cellular architecture, we can believe that a functional proteome is a prerequisite for regulating the essential physiological pathways and maintaining good cellular health. To preserve an advantageous proteome, the cells have a well-developed protein quality control (PQC) machinery that ensures a healthy set of proteins is called proteostasis. Chaperones are the first line of molecules that orchestrate most of the physiological and metabolic tasks and are significant components of the cellular QC pathways is presented in Fig. 1. QC pathways in this section. An intracellular overview of these pathways and their subsequent impact on the cellular physiology. At the same time, structural and computational biologists have played a critical role in providing crucial insights about the mysteries of the genetic codes, amino acid sequences, and structural plans of the proteins. Many other tools have also helped in devising various ways of visualizing and interpreting the intermolecular interactions involved in different cellular pathways and mechanisms.

In the past many years, substantial efforts have been made to affect the functional efficiency of many components of the PQC systems to establish and maintain the homeostatic conditions inside cells. Small molecules obtained from plants and other natural sources may have diverse medicinal values, as they can modulate many cellular proteins and affect several associated signaling pathways. The primary sources of these molecules of immense medicinal values include bacterial or fungal isolates, extracts of marine animals or plant sources, and few specific mammalian tissue secretions, etc. The upcoming sections describe the significance of these crucial cellular subsystems in regulating multiple molecular networks. The article further provides a brief overview of the available reports describing various naturally-derived molecules with the proposed medicinal values.

2. Cellular protein quality control system

A battery of multifaceted enzymes is involved in the replication and transcriptional processes, exhibiting highly efficient proof-reading activity to preserve the genomic contents of the cell. Similarly, in association with an array of extremely proficient molecular chaperones, a well-organized ribosomal quality control (RQC) machinery maintains the robustness of the cellular proteome. Additionally, a specialized pathway of quality assurance of newly synthesized polypeptides (called ERAD) operates inside the endoplasmic reticulum and associated secretory pathways. Several molecular chaperones and additional proteins get involved in these QC pathways, regulating the folding and degradation processes inside the cells and maintain a healthy and functional cellular proteome. All the cellular proteins have their unique turnover rate regulated by the ubiquitin-proteasome system (UPS) that involves a few hundred E3 ubiquitin ligase enzymes to provide the substrate specificity.

Under some physiological conditions, the E3 ubiquitin ligases, along with few other adapter proteins, may take part in identifying and redirecting aberrant or aggregated forms of intracellular proteins to another proteolytic pathway, called autophagy, which is not as specific as UPS and is chiefly take part in the degradation of the bulk of cellular debris. Similarly, heat shock proteins (HSPs) or molecular chaperones also play crucial roles in the triage of polypeptides inside the cytoplasm by switching among different quality control pathways. Here, we are providing a very brief outline of these major QC pathways in this section. An intracellular overview of these significant components of the cellular QC pathways is presented in Fig. 1.

2.1. Molecular chaperones

Proteins are large (macro-) molecules inside the cells, which orchestrate most of the physiological and metabolic tasks and are inclusively involved in the structural organization of the cellular components. Therefore, the maintenance of their native conformations is a prerequisite for the cells to be healthy. Such a condition of a stable and healthy set of proteins is called proteostasis. Chaperones are the first line of molecules that start their work immediately after the newly synthesized peptide exits from the ribosome. Different classes of molecular chaperones have already been reported in various forms of life across different kingdoms, including prokaryotes and eukaryotes. The de novo folding of nascent polypeptides is orchestrated by family chaperones and is accomplished by multiple cycles of ‘binding and release’ in an energy-dependent manner. Folding of a proportion of proteins is governed by HSP70 and HSP40,
whereas the rests of the proteins are transferred to HSP90 proteins. These chaperones are also implicated in refolding and disaggregating aberrantly folded polypeptides, or unfolding and degrading aggregated proteins. In fact, a large number of chaperones and chaperonins are coherently involved in the folding, refolding, and disaggregation processes of all the cellular proteins. Chaperones can guide the substrate proteins towards two well-established systems of proteins degradation, i.e., UPS and autophagy. They may interact with crucial proteins implicated in these two pathways, e.g., sequestosome-1 (SQSTM1/P62), BCL2 associated athanogene 1 or 3 (BAG1/3), carboxy-terminus of heat shock cognate 70 (HSC70) interacting protein (CHIP), next to BRCA1 gene 1 (NBR1), and several E3 ubiquitin ligases. The mechanisms that are driven by chaperones in concerted action with the other pathways are chaperone-mediated autophagy (CMA), chaperone-assisted selective autophagy (CASA), and chaperone-assisted proteasomal degradation (CAP).

2.2. Autophagy

The idea of autophagy originated in the 1960s when Christian de Duve identified lysosome, an organelle that contains hydrolytic enzymes, and got involved in removing cytoplasmic waste materials. Nobel Prize in Medicine to Christian De Duve in 1974, and Yoshinori Ohsumi in 2014 for the discovery of the lysosome and detailed investigation of this degradation pathway confirm the importance of the autophagy machinery for the cells. This lysosomal degradation process targets not only the damaged organelles but also different forms of cellular proteins, either ubiquitylated or non-ubiquitylated. Multiple lysosomal degradation pathways have been identified in the past with different roles and specificities; for example, the formation of a double-membrane bound structure, called the autophagosome, is a characteristic of macroautophagy that engulfs a large amount of cellular debris along with bulky proteinaceous inclusions.

Aggrephagy is often used to describe selective targeting of bulky protein aggregates or inclusion bodies for degradation.
through macroautophagy in a process facilitated by adapter proteins, like P62 and NBR1 and light chain 3 (LC3), a phagophore membrane receptor\textsuperscript{45,46}. A double-membrane structure called autophagosome is formed as a result of the closure of phagophore, which is followed by fusion with late endosomal vesicle or lysosomal sacs\textsuperscript{47,48}. The contents within this newly formed structure, referred to as amphisome, are degraded by various lysosomal enzymes\textsuperscript{49,50}. Similar to aggrephagy, few other pathways of selective degradation of cytoplasmic proteins are orchestrated by cytosolic chaperones HSC70 along with its regulatory co-chaperones\textsuperscript{51,52}. For example, microautophagy involves selective transport of cytosolic proteins to vesicles using endosomal sorting complexes required for transport (ESCRT I and III) in the HSC70-dependent manner\textsuperscript{53,54}. However, the microautophagy pathway involves invagination and tube formation, followed by vesicle expansion and degradation\textsuperscript{55,56}.

Another highly selective proteolytic pathway is CMA that could be defined as a process of selective identification of the KFERQ motif-containing cellular proteins by HSC70 and co-chaperones\textsuperscript{57,58}. The HSC70-conjugated substrates are internalized after binding to LAMP-2a (a lysosome-associated membrane protein) and later degraded by membrane-bound proteases\textsuperscript{59,60}. BAG3-mediated selective degradation pathway, CASA is also governed by chaperones HSC70 and HSPB8, in concerted action with CHIP (an E3 ligase) that mediates the ubiquitination of the proteins before their disposal to the lysosomal compartment in a P62-dependent manner\textsuperscript{61,62}.

2.3. Ubiquitin–proteasome system (UPS)

The ubiquitin–proteasome pathway is a multistep process of protein degradation, in which a series of enzymes sequentially catalyze the substrate proteolysis inside a large barrel-shaped, cylindrical protein complex called proteasome\textsuperscript{63,64}. The 20S proteasome is a multi-subunit complex containing a 20S core particle and one or two regulatory 19S sub-particles to regulate the entry of the ubiquitylated chains into the core\textsuperscript{63,64}. The 20S core proteasome subunit contains three types of protease activities governing the cleavage of incoming polypeptides into smaller fragments\textsuperscript{65,66}. Out of four heptameric rings forming the core, two
inner rings, termed β-rings, contain the proteolytic activities of
different types: post-glutamyl peptide hydrolase (β1), trypsin (β2),
and chymotrypsin (β5)95,96. In the first ATP-dependent step, an E1
ubiquitin-activating enzyme activates the small 8 kDa ubiquitin
molecule (Ub) and forms a thioester bond11,12. A transacylation
reaction transfers this ubiquitin to the thiol group present on
another class of enzymes called E2 ubiquitin-conjugating
enzyme3,24. These thiol esters (ubiquitin-E2 conjugates) provide
ubiquitin molecules to the third class of enzymes called E3
ubiquitin ligases for tagging the substrate proteins79,80. The
C-terminus glycine of the ubiquitin polypeptide forms an iso-
peptide bond with one of the lysine residues present on the cellular
proteins86.

According to the long-standing notion, attachment of single
ubiquitin (monoubiquitination) generally does not target substrate
proteins for proteolytic pathways; however, recent advancements
also oppose this belief77. In addition, more than one ubiquitin
molecules might get attached to the substrate proteins, independ-
ently (multi-monoubiquitination) or one over the other (poly-
ubiquitination) through lysine residues present in the already
conjugated ubiquitin or the N terminal methionine residue of
ubiquitin78. This may result in an array of signals, and ubiquitin
codes interpreted and dealt in different manners by cellular sub-
systems99,80. The patterns of attachment of subsequent ubiquitin
moieties may govern differential fates of the targeted proteins. For
example, a Lys-63 linked ubiquitin chain preferentially directs the
proteins towards autophagic degradation11,82. Contrarily, highly
abundant K-48 linked polyubiquitin chains are majorly targeted
for proteasomal degradation83. Other ubiquitin chains formed with
K6, K11, K27, K29, and K33 linkages form different kinds of
signals and regulate multiple physiological processes, including
cell cycle control, cellular transport, and DNA repair84–86.

Altogether, the involvement of the UPS has been reported in
immune pathways, hormonal signaling, cellular metabolism,
apoptosis, etc.10,87. Considering the coexistence of all these pro-
teolytic processes inside the eukaryotic cells, we can assume that
maintenance of proteostasis requires a very tightly regulated co-
ordination between different components and arms of the cellular
protein quality control85,89. Their involvement in the pathologies
of cancer, neurodegeneration, and aging processes has led scient-
ists to identify their therapeutic potential and devise methods or
ways to modulate them for exploitation for remedial purposes.
Natural molecules have remained a primary therapeutic tool over
the years showing enormous potential to modulate crucial regul-
atory proteins inside the cells. Several reports over the past few
years, as shown in Table 2, have been published describing various
kinds of possible regulation of different UPS components, which
ultimately govern many disease-associated pathways.

3. Pathological conditions affected by altered protein quality
control

Aging, neurodegeneration, and cancer have always remained
significant challenges before the scientific community. Many
theories and hypotheses have been formulated and postulated to
explain these pathologies, but none has succeeded in under-
standing why these pathological changes occur. Genetic, envi-
ronmental, infections and metabolic alterations are among the
many possible reasons behind most proteopathies10,91. However,
one of these could solely be held responsible for pathological
conditions; instead, a blend of multiple factors contribute towards
a highly diverse disease condition. This diversity among the in-
dividual cases of these pathologies further complicates the
research processes and leads to failure of treatment options92–94.
However, in the past few decades, tremendous progress is
observed in our understanding of many of these pathologies. At
the same time, these advancements have led to the evolution of
multiple lines of research methodologies and approaches to un-
derstand a given problem. This has given rise to speculations and
multiple lines of theories behind the origin, development, suste-
nance, and progression of these pathologies.

The declined competence of cellular defense mechanisms
and pathways are suggested to be one such notion that has
attained wide acceptance in recent decades2,3. Inefficient func-
tions of quality control systems that regularly monitor the well-
being of the genomic and proteomic repertoire of the cells could
be a possible cause of instigating multiple pathways leading
towards aging4. The compromised capacity of molecular chap-
erones to fold the nascent polypeptides into the proper three-
dimensional shape and deficient functioning of autophagy and
the proteasomal system could be credited for over-burdening the
cytosplasmic milieu with misfolded proteins95,96. Aggregation of
multiple types of aberrant proteins could lead to the formation of
large perinuclear/cytosplasmic inclusion bodies that may further
mount a heightened reaction by initiating immunological re-
sponses97. The increased burden of the aggregates may lead to
increased neuronal deaths, as observed in many disease models of
neurodegeneration98,99.

Aging encompasses several other attributes or hallmarks,
which may include but is not limited to the genomic instability,
mitochondrial loss, telomere shortening, metabolic alterations,
etc.91,100. These pathways and alterations in their physiological
conditions are also among the crucial factors responsible for most
types of cancers101,102. Altogether, the conditions discussed above
have many common features. One of the similarities is the
compromised proteostasis caused due to the inefficient protein
folding and degradation in cells103,104. Many other diseases, like
diabetes, cataract, cystic fibrosis, myopathies, etc. are directly
affected by the aggregation of one or more proteins2,105. An
imbalance in proteostasis may directly or indirectly link with many
other life-threatening diseases associated with lungs, heart, liver,
kidneys, etc.15,106. Based on the recommendations made by the
International Society of Amyloidosis, a depiction of various
amyloidogetic proteins, their aggregatory forms, and the affected
organs in many associated diseases is presented in Fig. 2107–109.
However, drawing a common line across all these diseases would
be difficult at the present state of our understanding of these
intracellular systems. Based on their common connecting links,
i.e., perturbed proteostasis and the cellular PQC machinery,
various strategies have been postulated in the past, while some are
currently under trial.

4. Small natural molecules: An effective therapeutic armory
targeting severe pathological conditions

Humans have learned the art of extraction and effectively uti-
lizing naturally occurring bioactive components and chemical
molecules towards medical purposes for centuries. Many
groundbreaking discoveries about the inherent medicinal prop-
erties of natural compounds against numerous life-threatening
diseases have been awarded Nobel Prizes in the past. The mid-
nineteenth century discoveries of antibiotics penicillin and
streptomycin have thoroughly changed the idea of drug discovery and accelerated the pursuit of more such compounds for other medicinal purposes in the following decades. Technological advancements, the inclusion of computational approaches, and the reincarnation of the vast literature of ancient Indian and Chinese medicine have substantially assisted and overwhelmed the field of drug discovery. The recent Nobel Prize for recognizing the medical importance of avermectins and artemisinin has again pressed upon the hidden potential of the small molecule-based drug substances.

In previous sections, we have discussed how the formation of inclusion bodies follows an aberrant protein aggregation. The inefficiency of cellular QC mechanisms to fight back and address the loss of proteostasis-like conditions may lead to an array of systemic

### Table 2

Small natural compounds having chaperone-modulating activities. A broad array of natural molecules have been identified over the years, which can enhance or suppress the cellular chaperoning activity by elevating the expression or interfering with the functioning of major chaperones belonging to HSP70, HSP90, small HSPs or co-chaperones.

| Compound | Source | Target protein | Target disease | Model system | Ref. |
|----------|--------|----------------|----------------|--------------|------|
| Actinomycin D | *Streptomyces parvulus* | HSP70 | Huntington’s disease | *S. cerevisiae* | 42 |
| Celastrol | *Tripterygium wilfordii* | HSF1, SSA3/4 | Stress response | *S. cerevisiae* | 43 |
| Compound A | Salsola tuberculatiformis | HSP70 | Inflammation | A549 cells | 44 |
| Curcumin | *Curcuma longa* | HSF1, HSP70 | Stress response | C6 cells, rats | 45 |
| Geldanamycin | *Streptomyces spp.* | HSP70 | Neurodegeneration | H4 cells | 46 |
| Glycyrrhizin | *Glycyrrhiza glabra* | HSP70 | Stress response | *HeLa* cells | 47 |
| Handelina | *Handelia trichophylla* | HSP70 | Neuroinflammation | BV2, HEK293T | 48 |
| Lanostanol | *Metabolic intermediate* | CHIP | Neurodegeneration | *Cos7* cells | 49 |
| Myricetin | Fruits and berries | HSF1, HSP70 | Stress response | *HeLa* cells | 50 |
| Paoniflorin | *Paeonia lactiflora* | HSF1, HSP70 | Stress response | *HeLa* cells | 51 |
| Prostaglandins | Human | HSF1, HSP70 | Stress response | C6 cells | 52 |
| Withaferin A | *Withania somnifera* | HSP25, HSP70 | ALS | *Mice* | 53 |
| **HSP90 inhibitors** | | | | | |
| Argentoside A | *Tabebuia argentea* | HSP90 | Epithelial carcinoma | *HeLa* cells | 54 |
| Celastrol | *Tripterygium wilfordii* | HSP90 | Prostate cancer | *LNCaP* cells | 55 |
| Clorobiocin | *Streptomyces spp.* | HSP90 | Breast cancer | SKBR3, MCF7 | 56 |
| Coumermycin A1 | *Streptomyces spp.* | HSP90 | Breast cancer | SKBR3, MCF7 | 57 |
| Cruentaran A | *Byssosorax cruenta* | HSP90 | Lung, breast cancer | A549, MCF-7 | 58 |
| Curcumin | *Curcuma longa* | HSP90 | Viral infection | *HELF* cells | 59 |
| Deggulian | *Derris trifoliata* | HSP90 | Cancer | *Mice* | 60 |
| Derrubone | *Derris robusta* | HSP90 | Breast cancer | SKBR3, MCF-7 | 61 |
| EgCG | *Camellia sinensis* | HSP90 | Hepatoma | HePa, HspG2 | 62 |
| Gambogic acid | *Garinia harburyi* | HSP90 | Cancer | SKBR3, MCF7 | 63 |
| Gedunin | *Azadirachta indica* | HSP90 | Prostate cancer | *LNCalp cells* | 64 |
| Geldanamycin | *Streptomyces spp.* | HSP90, HSF1 | Cancer | H3T cells | 65 |
| Herbinycin A | *Streptomyces spp.* | HSP90 | Cancer | H3T cells | 66 |
| Hypercin | *Hypericum spp.* | HSP90 | Squamous carcinoma | *SQ2* cells | 67 |
| Kotschyn D | *Astragalus lentiginosus* | HSP90 | Cancer | *In silico* | 68 |
| Macbein | *Actinomyces spp.* | HSP90 | Prostate, lung cancer | DU145, H460 | 69 |
| Monocillin I | *Monocillium nordii* | HSP90 | Breast cancer | MCF-7 cells | 70 |
| Novobiocin | *Streptomyces niveus* | HSP90 | Breast cancer | SKBR3, MCF-7 | 71 |
| Pochonins | *Pochonia chlamydospora* | HSP90 | Cancer | *In vitro* | 72 |
| Radiocil | *Monosporium bonorden* | HSP90 | Cancer | NH3T3 cells | 73 |
| Sansalvamide A | *Fusarium spp.* | HSP90 | Colon cancer | HCT-116 | 74 |
| Withanolides | *Withania somnifera* | HSF1, HSP90 | Thyroid cancer | *DRO, NPA* cells | 75 |
| Quercetin | Fruits and berries | HSF1, HSP90 | Breast cancer | *HeLa* | 76 |
| Triptolide | *Tripterygium wilfordii* | HSP90 | Cancers | *HeLa* cells | 77 |
| **HSP70 inhibitors** | | | | | |
| Apidaecin | Insect peptides | DNAK, GROEL | Microbial infection | *E. coli* | 78 |
| Cantharidin | *Epicauta funebris* | HSP70 | Colorectal cancer | HCT-116 cells | 79 |
| Drosopepin | Insect peptides | DNAK, GROEL | Microbial infection | *E. coli* | 80 |
| Fisetin | Fruits and berries | HSP70, HSF1 | Colorectal cancer | HCT-116 cells | 81 |
| Myricetin | Fruits and berries | DNAK | Colorectal cancer | HCT-116 cells | 82 |
| Novolactone | Fungal metabolites | HSP70 | Colon cancer | HCT-116 cells | 83 |
| Pycnocrin | Insect peptides | DNAK, GROEL | Microbial infection | *E. coli* | 84 |
| Quercetin | Fruits and berries | HSP70, HSF1 | Proteostasis | BHK cells | 85 |
| adasGC | Fungi | HSP70 | Lung cancer | A549, H460 cells | 86 |
| Spergulain | *Bacillus subtilis* | HSC70 | Immune reaction | Jurkat cells | 87 |
| Triptolide | *Tripterygium wilfordii* | HSF1, HSP70 | Cancers | *HeLa, HEK293T* | 88 |
| Tubocapsenolid A | *Tubocapsicum anomalous* | HSP90-HSP70 | Breast cancer | MDA-MB-231 | 89 |
and non-systemic diseases. With the available knowledge and experimental evidence, it could be understood that reestablishing the lost activities of these pathways, by inducing chaperone function or enhancing the activities of proteolytic machinery (proteasome and autophagy), etc., may exhibit the tremendous potential to delay the onset of pathologies or aging-associated changes inside the organ-isms. Results from many studies converge towards the consensus advocating for small molecule-based therapies as beneficial and low-cost strategic tools to suppress the aggregation of most kinds of disease-associated amyloidogenic aggregates. Notably, many recently recognized molecules, termed as pharmacological chaperones, have a strong potential of precisely facilitating the folding and stabilization of aberrant proteins, thereby assist in restoring their native functions.

The bulk degradation pathway of the cells, termed as ‘autophagy’ soon after its discovery by Christian de Duve, derived its name from Greek words meaning self-eating. In later years, it was found that the autophagic degradation, which was initially considered a non-specific degradation system of the cells, could also be a part of much-targeted protein degradation pathways in association with chaperones or UPS components. It joins hands with the UPS and plays a balancing act of degradation with the protein synthesis and folding machinery concurrently working in the cells. Many studies also suggest that autophagy and proteasome pathways may also compensate each other under different stress conditions; therefore, a few drugs suppressing UPS activity, e.g., MG132 and lactacystin, may lead to activation of autophagic responses. Contrarily, inhibition of autophagy overwhelms the cells with accumulating protein inclusions causing impairment of proteasomal degradation. In truth, a clear understanding of how the two systems balance each other while protecting the cells from proteotoxic stresses is not known. Here, a comprehensive overview is provided for those molecules or drug candidates, which can bind and modulate the activity or functions of one or multiple cellular PQC machinery components.

4.1. Modulating cellular chaperoning potential: Provides additional buffer against stress conditions

Chaperones are essential regulators of cell homeostasis, and their anomalous functioning can lead to perturbation of many normal and stress-related pathways. The primary functions that the HSP family proteins perform inside the cells are recognizing any unusual change in the cellular homeostasis, encountering spontaneous stress condition, and providing a piece of machinery to

Figure 2  An overview of amyloidosis. Various amyloid-forming proteins (left), their normal precursor protein forms (middle), and tissues or organs affected in one or more similar diseases caused by individual proteins. The left column shows a list of amyloidic forms of various proteins shown in the center as precursors. These proteins may aggregate in such amyloidic structures in their full, cleaved, or modified forms, while several mutations contribute to their amyloidogenicity. The structural modification of these proteins may lead to abnormal metabolic or signaling alterations at the molecular level in different tissues and organs. These changes may lead to a possible functional loss or decline, causing multiple pathological conditions. Many proteins are found to be involved in multiple diseases of different organs, whereas some diseases may have several proteins involved together in the pathogenesis. The figure was prepared using RAWGraphs, an open source platform for data representation (http://rawgraphs.io).
The associated diseases and studied model systems are also presented in adjacent columns. The associated diseases and studied model systems are also presented in adjacent columns.

| Compound | Source | Subunit | Pathway/disease | Model system | Ref. |
|----------|--------|---------|----------------|--------------|-----|
| Betaeinic acid | Betula sp. | β5 | Neurodegeneration | MT4 cells | 84 |
| Canthinn-6-one | Alkanthus alitissima | β5 | Parkinson's disease | Mice | 85 |
| Fatty acids | Animal sources | β1 | Ageing | Rats | 86 |
| Harmine | Animal sources | β2 | Ageing | Human erythrocytes | 88 |
| Lyso sphospholipids | Animal sources | β5 | Acrosome formation | Sea urchin sperm | 89 |
| Oleuropein | Oilea europea | β1, β2, β5 | Ageing | IMR90, WI38 cells | 90 |
| Oxophylla A | Alpinia oxypylla | β5 | Parkinson's disease | Mice | 91 |
| Sulfonides | Animal sources | β5 | Ageing | Human erythrocytes | 88 |
| Sulforaphene | Brassica oleracea | β1, β2, β5 | Neurodegeneration | Mice | 92 |
| Zernobone | Zingiber zerumbet | β5 | Neurodegeneration | Hepa1c1c7 cells | 93 |

### Proteasomal inhibitors

| Compound | Source | Subunit | Pathway/disease | Model system | Ref. |
|----------|--------|---------|----------------|--------------|-----|
| Aaptamine | Aaptops suberitoides | β1, β5 | Cancer | HeLa cells | 94 |
| Acaarubicin | Streptomyces galilaeus | β5 | Cancer | Bovine pituitary | 95 |
| Agosterol C | Spongia sp. | β5 | Cervical carcinoma | HeLa cells | 96 |
| Antiprotealide | Salinispora tropica | β5 | Multiple myeloma | RPMI 8226 cells | 97 |
| Argynin A | Archangium glypha | β1, β2, β5 | Cancer | HeLa, SW480 cells, mice | 98 |
| Belactosin A/C | Streptomyces sp. | β5 | Muscle wasting | Rats | 99 |
| Carmaphycin-17 | Symplocos sp. | β1, β7 | Trichomoniases | Trichromonas vaginalis | 100 |
| Ciclosporine A | Tolypocladium inflatum | β5 | Inflammation | RAW, murine brain | 101 |
| Cinnarabimides | Streptomyces sp. | β5 | Cancer | PBMC cells | 102 |
| Cystargolide A | Kitasatospora cystarginea | β5 | Cancer | Purified 20S proteasome | 103 |
| Dibromophakellin | Phakellia flabellata | β1, β5 | Cancer | HeLa cells | 104 |
| Epoxymycin | Streptomyces sp. | β5 | Murine thymoma | EL4 cells | 105 |
| Epoxymycin | Actinomyces sp. | β2, β5 | Inflammation | HUVEC cells | 106 |
| Fellutamide B | Penicillium fellutanum | β5 | Nerve injury | Mouse fibroblasts | 107 |
| Glidobactins | Polysaccharide brachyosporum | β2, β5 | Cancer | Phaseolus vulgaris | 108 |
| Gliotoxin | Aspergillus fumigatus | β5 | Cancer | HeLa cells | 109 |
| Halicyclamine B | Halicionia sp. | β1, β2, β5 | Cancer | HeLa cells | 110 |
| Heteronemin | Hyrtios sp. | β2, β5 | Leukemia | K562, Jurkat T cells | 111 |
| Lactacystin | Streptomyces lactaccyrticus | β1, β2, β5 | Neuroblastoma | Neuro2a | 112 |
| Lovastatin | Pleuortus ostreatus | β5 | Breast cancer | MDA-MB-157 cells | 113 |
| Marizobin | Salinospora sp. | β5 | Colon carcinoma | HCT-116 | 114 |
| Mevatatin | Penicillium citinum | β5 | Neuroblastoma | NB2 cells | 115 |
| Mycolalides | Mycale sp. | β5 | Neuroblastoma | Neuro2a | 116 |
| Omuralide | Streptomyces sp. | β5 | Neuroblastoma | HeLa cells | 117 |
| Palamine | Stylophora aequinata | β5 | Cancer | NIH-3T3 cells | 118 |
| Petrosaspigonioides M | Petrosaspigonia nigra | β1, β5 | Inflammation | THP cells | 119 |
| Rhabdastrellic acid-A | Rhabdastrella globostellata | β2, β5 | Leukemia | HL-60 cells | 120 |
| Syringolins | Pseudomonas syringae | β1, β2, β5 | Cancer | Phaseolus vulgaris | 121 |
| TMC-95 | Apiospora montagnei | β1, β5 | Cancer | HCT-116, HL-60 cells | 122 |
| Tyropeptin A | Kitasatospora sp. | β2, β5 | Cancer | HeLa cells | 123 |

### Plant products

| Compound | Source | Subunit | Pathway/disease | Model system | Ref. |
|----------|--------|---------|----------------|--------------|-----|
| Ajoene | Allium sativum | β2, β5 | Leukemia | HL-60 cells | 124 |
| Apigenin | Portulaca oleracea | β5 | Breast cancer | MDA-MB-231, mice | 125 |
| Bisibenzyls | Bryophytes | β5 | Prostate cancer | LNCaP cells | 126 |
| Capsaicin | Capsicum annum | β1, β2, β5 | Prostate cancer | PC-3 cells | 127 |
| Celestrol | Tripterygium wilfordii | β5 | Prostate cancer | PC-3 cells, mice | 128 |
| Chrysin | Passiflora caerulea | β2, β5 | Cancer | HepG2, HL-60, A549 | 129 |
| Curcumin | Curcuma longa | β1, β2, β5 | Cancer | Neuro 2a cells | 130 |
| Catechin-gallate | Camellia sinensis | β5 | Cancer | Jurkat T cells | 131 |
| Emodin | Rheum palmatum | β1, β2, β5 | Cancer | HeLa cells, mice | 132 |
| Fangchinoline | Stephania tetrandra | β1 | Breast cancer | LNCaP, PC-3 cells | 133 |
| Genistein | Glycine max | β5 | Cancer | LNCaP, MCF-7 cells | 134 |
| Gynenosides | Panax ginseng | β5 | Cancer | RBCs | 135 |
| Isoginkgetin | Ginkgo biloba | β1, β2, β5 | Cancer | HeLa cells | 136 |
| Kaempferol | Fruits and vegetables | β5 | Leukemia | Jurkat T cells | 137 |
| Luteolin | Cichorium endivia | β2, β5 | Cancer | HepG2, HL-60, A549 | 138 |
| Marchantin M | Marchantia sp. | β1, β5 | Prostate cancer | PC-3 cells | 139 |
monitor and establish the structures and functioning of other cellular proteins. The term ‘chemical chaperone’ has been widely used in the past decade for a group of potentially active molecules that can stabilize cellular proteins in a non-specific way and help in reversing the mislocalization or aggregation. These molecules mostly act on the proteins’ active domains or sites, providing them an increased opportunity to form hydrogen, electrostatic, and van der Waals interactions and potentially stabilize the overall structure of the proteins. Additionally, an array of naturally occurring substances and their derivatives have shown modulatory potential over inherent chaperoning capacity inside the cells.

These bioactive chemical molecules can bind and alter the structure, activity, and overall functions of the most active HSP70 and HSP90 chaperone complexes, along with many of their co-chaperones and accessory factors. They also provide cushion for structural rearrangements of unfolded or misfolded proteins inside the cytosol, thus help in ameliorating the accumulation of aberrant proteins. However, the initial attempts to exploit chaperones for therapeutic purposes started with identifying the inhibitory activity of radicicol against HSP90 ATP-binding pockets. It was initially used against malignant fibroblasts. Although promising, the drug failed in delivering the promises because of several pharmacokinetic challenges. The other prominent molecule in this category is a bacterial isolate geldanamycin that was later proved to be toxic to the liver. In later years, advancements in the medicinal chemistry tools have led to the synthesis of many derivatives of these less successful drug candidates, e.g., monocillin I, pochonins, 17-allylamino-geldanamycin (17-AAG), etc.

Small molecules can shatter the interaction of major chaperones with their co-chaperones, thereby affecting chaperoning activities. For example, celestrol, a triterpene, and gambogenic acid, a xanthonoid, can interfere with the interaction of HSP90 with its co-chaperone CDC37; while curcumin blocks HSP90–P23 binding, leading to the induction of cell death signaling pathways. Other drug candidates with similar cell death-inducing effects are herbimycin A and derrubone. Quercetin, one of the most studied flavonoids, shows an upstream regulation of heat-shock response inside the cells by suppressing the heat shock factor (HSF1), the major transcription factor that regulates the intracellular levels of most of the chaperones. A green tree extracted molecule, epigallocatechin-3-gallate (EGCG), can also inhibit multiple chaperones, including HSP90, HSP70, and ER-resident GRP78, and suppress the growth of cancer cells. Interestingly, other mechanisms of functional suppression of HSP90 are increased ubiquitination (by hypericin), destruction of chaperone cycle (by sansalvamide A), and oxidation (by tubocapsenolide A) of HSP90 itself. All these can interfere with the turnover of the substrate proteins of the chaperones, thus deregulating the proteostasis balance of the cell.

Modulation of HSP70 functions by myricetin and spregualin may also help suppress cancerous cells’ growth, possibly by inhibiting the ATPase activity of the chaperone. Few reports further suggest the possible activation of upstream regulator HSF1 in response to drug-mediated suppression of one or the other molecular chaperones; however, more work is required to understand the feedback mechanisms involved in this mechanism. A few studies have shown that geldanamycin-mediated HSP90 inhibition may, in turn, upregulate the activities of HSP70 and HSP40, which could be helpful and may benefit the neuronal cells under different stress or pathology conditions, e.g., HD, ALS, cerebral ischemia, etc. Similarly, treatment of curcumin and withafarin A may also exert neuroprotective effects on the cells and mouse models; the effects could be due to improved activities of HSP70, HSP27, and α-crystallin chaperones. A summarized overview of various such kinds of molecules of natural origin that can help in reestablishing the proteostasis inside the cells by modulating the inherent chaperoning capacity of the cell has been presented in Table 3.

4.2. Regulating the UPS components: Playing with the fine balance

UPS is the next line of defense in most subcellular compartments and works continuously to regulate the proteostasis inside these organelles. As described previously, ubiquitination and proteasomal degradation are a kind of intracellular regulatory mechanisms that often is crucial for many cellular pathways. Therefore, any disturbances in these systems may have deleterious effects on cellular health. The proteasomal system comprises several components that could be regulated by different mechanisms and may exert varying effects on cellular physiology. For example, regulating the activities of proteasomal subunits has been shown to have a direct effect on the overall cellular protein degradation scheme and the overall proteostasis. Many proteasome modulators have been proposed, and a few of them are under clinical trials for diseases like cancer and neurodegeneration. A plethora of naturally-derived chemicals has been reported over the years, which have shown a substantial modulation of the activities of various enzymes of the pathway. Thus, their use may enhance or suppress the proteostasis provided by these enzymes.
The proteasomal system is very specific in its activity and takes part in the precise regulation of the majority of physiological pathways; therefore, very tightly-controlled modulation is needed in order to exploit it for therapeutic purposes\textsuperscript{153,154}. Bortezomib was the initial drug having the proteasomal inhibitory potential and has been widely used as an anticancer drug for long\textsuperscript{155}. Later, another synthetic molecule, carfilzomib, was also approved by the U.S. Food and Drug Administration (FDA) for anti-cancer therapy\textsuperscript{160}. Following the identification of these two FDA approved drugs, many other drugs with similar inhibitory activity against different proteolytic subunits (\(\beta_1\), \(\beta_2\), and \(\beta_5\)) of 20S proteasome have been identified and thoroughly investigated for their therapeutic applications in many diseases\textsuperscript{161,162}. Lactacystin is the most well-known natural molecule of this class that was initially reported to be effective against neuroblastoma cells and is currently one of the widely used drugs in the research\textsuperscript{163}. Eponemycin and epoxymycin specifically target chymotrypsin-like activity containing \(\beta_5\) subunits of the 20S core and help in suppressing the inflammation in cancer cells\textsuperscript{164,165}. Mevastatin, belactosin A, and fellutamide B are other similar bacterial isolates that have been presented with the anti-protease activity of the proteasome in different experimental model systems\textsuperscript{166--168}.

Fungi and marine animals are other prominent sources of many biologically active molecules having critical therapeutic properties. Many proteasomal inhibitors have been isolated from these animals also. For example, gliotoxin and cyclosporine A from fungal sources and agosteryl C and aptamine from sponges are prominent inhibitors of 20S proteases\textsuperscript{169--172}. These molecules could affect one or multiple protease subunits of the 20S core particle of the proteasome. Interestingly, the toad venom contains a compound called arenobufagin that has the potential to inhibit all three activities simultaneously\textsuperscript{173}. An exhaustive list of such natural molecules obtained from various biological sources has been presented in the form of Table 3. Plant-based molecules have specifically dragged lots of attention for their proteasome-modulatory activity and have been widely covered in other descriptive reviews\textsuperscript{174,175}.

Flavonoids make the most comprehensively explored class and have shown tremendous potential to be used in therapeutics against many diverse kinds of diseases. For example, genistin, EGCG, and physalin B have anti-cancerous roles, while pectolinarin has positive effects on tuberculosis due to its anti-inflammatory potential\textsuperscript{176--178}. Apigenin, myricetin, quercetin, and luteolin are anti-atherogenic and may also help suppress tumor growth\textsuperscript{179--182}. PM15011 is an ethanolic preparation obtained from a herb, Artemisia dracunculus, and shows pathological improvements in diabetes mice\textsuperscript{183}. Polyphenols like vinblastine, capsaicin, resveratrol, tamic acid, and curcumin\textsuperscript{184--186}, along with some well-known terpenoids, e.g., celestrol, pristimerin, etc., further adds up to the list\textsuperscript{187,189,190}. The compounds like amthraquinones, saponins, sulfur-derivatives, and plant-derived lactones come next into this long list (Table 3) of compounds with different types of inhibitory potential against \(\beta_1\), \(\beta_2\), or \(\beta_5\) activities of proteasome.

Contrary to proteasomal suppression, which is widely exploited in cancer therapeutics, enhancing the proteasomal activities could be useful in many stressful conditions and in the diseases associated with protein misfolding and aggregation. Two widely explored terpenoids, zerumbone and betulinic acid, have activated the \(\beta_5\) activities and thus presented neuroprotective effects\textsuperscript{191,192}. Myricetin, oleuropein, and sulfureaphane are other plant-derived molecules representing the proteasomal activators that may upregulate one or multiple 20S core subunits\textsuperscript{193,194}. Few other molecules were identified that might delay the aging and neurodegenerative processes by increasing proteasomal degradation of the substrate proteins. These are heparin, sulfatides, and lysosphospholipids, a few metabolic byproducts or those obtained from other animal sources\textsuperscript{195,196}. Unlike proteasome inhibition, the effects of proteasome activation are not widely explored and need a more rigorous investigation to identify new molecules with a positive effect on proteasome functioning and their downstream impact on protein clearance.

A few recent studies have given clear insights into Parkinson’s disease models that activation of proteasome function by hermine, oxyphylla A, and canthin-6-one can significantly upregulate the clearance of alpha-synuclein, the major constituent of the Lewy bodies formed in the substantia nigra\textsuperscript{197,198}. Apart from proteasome subunits of 20S particle, many other components involved in protein ubiquitination have been looked for their applicability as a possible drug target in aging, neurodegeneration, and many other diseases. Modulation of the major enzymes involved in the ubiquitination process, e.g., E1, E2s, E3s, and deubiquitinas (DUBs), could be a vital strategy to regulating several critical signaling and metabolism pathways\textsuperscript{19,200}. E1 ubiquitin-activating enzyme is a unique protein required for the ubiquitination of all the possible cellular substrate proteins. Therefore, interfering with its activity may compromise the whole UPS and may have devastating effects\textsuperscript{11}. However, this observation can be utilized in anticancer therapeutics as previously exemplified by hyrttiorieticulins largazole, himeic acid A and panepophenanthrin\textsuperscript{201--204}.

The next line of drug targets is E2 ubiquitin-conjugating enzymes, which transfer ubiquitin molecules from the E1 enzymes to the E3 ligases. Not too many drugs have been identified, which can interfere with the enzymatic activities of E2; however, a few known naturally-occurring compounds are vetixin, a polyphenolic extract from Byrsonima crassifolia, and a few poriferan-derived leucetamol A, manadoesters A and B, etc.\textsuperscript{205--207}. Deubiquitinas (DUBs) are a group of enzymes that are crucial for breaking down the ubiquitin chains, replenishing the ubiquitin pool of the cells, and playing regulatory roles in many biological pathways\textsuperscript{208,209}. Betulinic acid and one curcumin analog are a few known inhibitors of this class of enzymes, which have shown tremendous promises as anti-cancer molecules\textsuperscript{210,211}. Cruciferous vegetables have a group of compounds called isothiocyanates, which are prominent inhibitors of DUBs, and have shown significant anti-tumor properties\textsuperscript{12}. A diterpenoid candidate, 15-oxospiramialactone, is another DUB inhibiting molecule that has a positive effect on the restoration of the mitochondrial network\textsuperscript{212}.

Interestingly, the molecules that have the potency to modulate the most diverse class of enzymes of this pathway, the E3 ubiquitin ligases, has widely been explored for specific regulation of substrates and related pathways\textsuperscript{13}. However, some molecules may inhibit multiple E3s simultaneously. Hectin is a recently developed molecule that can suppress many HECT domain-containing E3 ligases. Additionally, a few ubiquitin variants were prepared, which have shown tremendous inhibitory potential against RING and U-box domains of the E3 ligases\textsuperscript{215--217}. A line of studies proposes several natural molecules as probable drug candidates against many life-threatening diseases. Inhibition of Mdm2 by matrine at the RNA level and by berberine via self-ubiquitination mechanism are prominent examples of regulating the turnover of P53, the primary tumor suppressor protein\textsuperscript{218,219}. Oxorolvin-A, apigenin, and genistein are plant flavonoids that may initiate a high apoptotic response in cancerous cells\textsuperscript{220--222}. Many terpenoids (e.g., triptolide, imulanolide, etc.), saponins, chalcones, and polyphenols extracted from
therefore can target specific molecular targets and pathways that are involved in many harmful diseases. Altering the autophagic flux, increase the protein degradation or interfere with different steps of autophagosome biogenesis or lysosome fusion, therefore can target specific molecular targets and pathways that are involved in many harmful diseases.

### Table 4: Small natural molecules affecting the cellular autophagy pathway. A concise representation of the potential candidates that can alter the autophagic flux, increase the protein degradation or interfere with different steps of autophagosome biogenesis or lysosome fusion, therefore can target specific molecular targets and pathways that are involved in many harmful diseases.

| Compound      | Source                     | Target pathway | Physiological condition | Model system | Ref. |
|---------------|----------------------------|----------------|-------------------------|--------------|------|
| Actinonin     | Streptomyces sp.           | AMPK, mRNA     | Cancers                 | HeLa cells   | 146  |
| Araguspongine C | Xestospongia sp.    | PI3K/AKT/mTOR  | Breast cancer           | BT-474 cells | 147  |
| Chromonycin A2 | Streptomyces sp.          | LC3           | Melanoma                | MALME-3M cells | 148  |
| Clionamine B  | Cliona celata             | LC3           | Breast cancer           | MCF-7 cells  | 149  |
| Coibamide A   | Leptolyngbya sp.          | LC3           | Glioblastoma            | U87-MG cells | 150  |
| Hirutosanol A | Chondrostereum sp.        | LC3           | Hepatic carcinoma       | Hep3B cells  | 151  |
| Ilimauquinone | Hipspongisia sp.          | p53           | Colon cancer            | RKO cells    | 152  |
| Isonapantamine| Aaptos sp.                | LC3           | Breast cancer           | T-47D cells  | 153  |
| Monanchoxin D | Monanthora pulchra        | P38, ERK      | Germ cell tumors        | NCCIT cells  | 154  |
| Overholt大海 | Paracenonotus lividus      | Beclin-1, LC3 | Hepatic carcinoma       | HepG2 cells  | 155  |
| Papainine     | HalicIonica sp.           | LC3, JNK      | Breast cancer           | MCF-7 cells  | 156  |
| Psammatin A   | Psammaplystila sp.        | P73           | Glioblastoma            | U87-MG cells | 157  |
| Rapamycin     | Streptomyces hygropicus   | mTOR          | Polyglutamine diseases  | PC12, Cos7 cells | 158  |
| Rhabdastrelic acid A | Rhabdastrella              | AKT           | Various human cancers   | Hep3B, A549 cells | 159  |
| Salinosporamide A | Salinospora tropica      | elf2α         | Prostate cancer         | LNCaP-Pro5  | 160  |
| Stelliton B   | Jaspsp stellifera         | PI3K/AKT/mTOR | Lung cancer             | A549 cells   | 161  |
| SD118-xanthicilin-X | Penicillium commune      | MEK/ERK       | Hepatic carcinoma       | HepG2 cells  | 162  |
| Trehalose     | Streptomyces cerevisiae   | mTOR          | Neurodegeneration        | SK-N-SH, PC12 cells | 163  |
| Urolithin A   | Gut microbeome            | AMPK          | Ageing                  | C. elegans   | 164  |
| Xestospongine B | Xestospongia exigua      | IP3, R        | Cervical adenocarcinoma | HeLa cells   | 165  |
| **Plant products** | **Plant products**        | **Target pathway** | **Physiological condition** | **Model system** | **Ref.** |
| **Terpenes**  |                           |               |                         |              |      |
| Bigelovin     | Inula helianthus          | AKT/mTOR/S6K  | Liver cancer            | HepG2, mice  | 166  |
| Erioclyxan B  | Isodon erioclyx          | AKT/mTOR/S6K  | Breast cancer           | MCF-7, MDA-MB-231 | 167  |
| Gossypol      | Gossypium sp.             | Beclin-1, ATG5, | Breast adenoecarcinoma  | MCF-7, HeLa cells | 168  |
| Grifolin      | Albatrellas confuence     | AKT/mTOR/S6K  | Ovarian cancer          | A2780, SKOV3 cells | 169  |
| Oridonin      | Rabdosia rubescens       | P21           | Prostate cancer         | PC-3, LNCaP cells | 170  |
| Platycodin-D  | Platycodon grandiflorum  | PI3K/AKT/mTOR | Lung cancer             | NCI-H460, A549 cells | 171  |
| Triptolide    | Tripterygium willofordii  | mTOR          | Neurodegeneration        | SK-N-SH, PC12 cells | 172  |
| Ursolic acid  | Ocimum sanctum            | JNK, BCL-2    | Colorectal carcinomas   | HCT-15 cells, mice | 173  |
| **Flavonoids** | **Flavonoids**            | **Target pathway** | **Physiological condition** | **Model system** | **Ref.** |
| Ampelopsis    | Ampelopsis sp.            | AKT/mTOR/S6K  | Breast cancer           | MDA-MB-231, MCF-7 | 174  |
| Apigenin      | Fruits, vegetables        | mTOR, S6      | Leukemia                | HL60, TF1 cells | 175  |
| Curcumin      | Curcuma longa             | FOXO1, beclin-1 | Oxidative stress        | HUVEC cells | 176  |
| Deliciaflavone | Selaginella doederleini  | AKT/mTOR/S6K  | Breast cancer           | A549, PC-9 | 177  |
| 5-Demethylobutein | Sideritis tragergamanum  | JNK           | Lung cancer             | A549 and CL-1-5 cells | 178  |
| Galangin      | Alpinia officinarum       | P53           | Hepatic carcinoma       | HepG2 cells  | 179  |
| Glabridin     | Glycyrrhiza glabra       | JNK1/2, P38, ERK | Hepatoma                | HepG2 cells  | 180  |
| Juglalin      | Juglans mandsharica      | JNK           | Breast cancer           | MCF-7 cells, mice | 181  |
| Kaemperol     | Fruits and berries       | AMPK, AKT     | Hepatic cancer          | SK-HEP-1 cells | 182  |
| Licochalcone A | Glycyrrhiza sp.          | AKT/mTOR/S6K  | Cervical cancer         | SiHa cells | 183  |
| Luteoloside   | Gentiana macrophylla     | AKT/mTOR/S6K  | Lung cancer             | A549, H292 cells | 184  |
| Myricetin     | Fruits, vegetables       | mTOR          | Hepatic carcinoma       | HepG2 cells  | 185  |
| Quercetin     | Fruits and berries       | PI3K, beclin-1 | Leukemia                | P39 cells, mice | 186  |
| Resveratrol   | Vitis viniferae          | SIRT1, RAB7   | Oxidative stress        | Mice | 187  |
| **Alkaloids** | **Alkaloids**             | **Target pathway** | **Physiological condition** | **Model system** | **Ref.** |
| Berbine       | Coptidis Rhizoma         | AKT/mTOR, beclin-1 | Hepatic carcinoma       | HepG2, MHCC97-L cells | 188  |
| Capsaicin     | Capsicum annuum          | Beclin-1, LC3 | Hepatic carcinoma       | HepG2 cells | 189  |
| Coryoxine B   | Uncaria rhynchophylla    | Beclin-1      | Parkinson’s disease     | N2a,SHSY-5Y cells | 190  |
| Fangchinoline | Stephania tetrandra      | Sestrin2      | Hepatic carcinoma       | HepG2 cells | 191  |
| Harmol A      | Peganum harmala          | Survivin      | Glioma                  | U251MG cells | 192  |
| Isohynochynoline | Uncaria rhynchophylla   | Beclin-1      | Parkinson’s disease     | N2a, PC12, SH-SY5 | 193  |
| Matrine       | Sophora flavescens       | mTOR, P53     | Hepatic carcinoma       | HepG2, SMMC-721 | 194  |
| Piperlongumine | Piper longum             | AKT/mTOR      | Various cancers         | 786-O, PC-3, MCF7 | 195  |
| Vinblastine   | Vinca rosea              | Cathespin D   | Stress conditions        | Rat hepatocytes | 196  |
| **Other natural molecules** | **Other natural molecules** | **Target pathway** | **Physiological condition** | **Model system** | **Ref.** |
| Areobufagin   | Toad venom               | PI3K/AKT/mTOR | Breast cancer           | HepG2 cells | 197  |
| Benzyliothiocyanate | Lepidium sativum      | AKT, mTOR     | Prostate cancer         | Rv-1, PC-12 cells | 198  |
| Bisbichenyls  | Bryophytes               | LC-3          | Prostate cancer         | LNCaP cells | 123  |

(continued on next page)
Table 4 (continued)

| Compound                  | Source               | Target pathway   | Physiological condition | Model system    | Ref. |
|---------------------------|----------------------|------------------|-------------------------|-----------------|------|
| Bufalin                   | *Bufo gargarizans*   | JNK, ATG5, beclin-1 | Colorectal cancer       | HT-29 and Caco-2 cells | 199  |
| Cinobufagin               | *Bufo gargarizans*   | PARP, JNK/P38     | Osteosarcoma            | U2OS cells      | 200  |
| Concanavalin A            | *Canavalia ensiformis* | LC3, BNIP3, AKT  | Hepatoma                | ML-1 cells      | 201  |
| Daucosterol               | *Smilax glabra Roxb.* | Beclin-1, LC-3   | Breast cancer            | MCF-7 cells     | 202  |
| Docosahexaenoic acid      | Metabolic intermediate | NFE2L2           | Neurodegeneration        | ARPE-19         | 203  |
| Embelin                   | *Embelia ribes*      | ATG-5, ATG-12    | Oral cancer              | Ca9-22 cells    | 204  |
| Lanosterol                | Metabolic intermediate | CHIP             | Neurodegeneration        | Cos-7           | 49   |
| Noggin                    | *Xenopus*            | LC3, beclin-1    | Acute pancreatitis       | AR42J cells, mice | 205  |
| Ophiopogonin B            | Radix ophiopogon var. | P3K/ATK/mTOR     | Lung cancer              | NCI-H157, NCI-H460 | 206  |
| Polyphyllin G             | *Paris yunnanensis*  | AKT, MAPK        | Nasopharyngeal carcinoma | HONE-1 and NPC-039 | 207  |
| Rottlerin G               | *Mallotus philippinensis* | P3K/ATK/mTOR    | Pancreatic cancer        | Cancer stem cells | 208  |
| 6-Shogaol                 | *Zingiber officinale* | AKT/mTOR         | Lung cancer              | AS49            | 209  |
| Sitosterol                | Plant sterols        | P38              | Sirotosteloma            | Mice macrophages | 210  |
| Spermidine                | Natural polyamine    | ATG7             | Ageing                   | Yeast, fly, worm, PBMC | 211  |
| Sulforaphane              | *Brassica oleracea*  | ERK              | Huntington’s disease     | Mice            | 212  |

### Autophagy inhibitors

| Asparagine                | Natural amino acid  | Lysosome fusion | Proteopathies           | Rat hepatocytes | 213  |
| Cytochalasin              | Aspergillus sp.     | Microfilaments  | Proteopathies           | Rat kidney cells | 214  |
| Emodin                    | *Fallopia japonica* | LC3, beclin-1   | Acute pancreatitis      | Rats            | 215  |
| Estrogen                  | Natural hormone     | CXCL12          | Endometriosis           | Endometrial stromal cells | 216  |
| Leupeptin                 | *Streptomyces sp.*  | Serine proteases| Proteopathies           | Rat hepatocytes | 217  |
| 3-Methyladenine           | Metabolic intermediate | P3K             | Proteopathies           | Hepatocytes     | 218  |
| Pepstatin A               | *Streptomyces sp.*  | Aspartyl peptidases | Proteopathies         | Rats, hearts | 219  |
| Vinblastine               | *Catharanthus rosea* | Microtubules   | Proteopathies           | Rat fibroblasts | 220  |
| Vincristine               | *Catharanthus rosea* | Microtubules   | Proteopathies           | Rat fibroblasts | 220  |
| Wortmanninin              | *Penicillium sp.*   | P3K             | Acute pancreatitis      | Rats            | 221  |

4.3. Natural modulators of autophagic pathway: Boosting the cellular stress response

The autophagic pathway was initially identified as an intracellular lysosomal degradation mechanism that targets consumed, unusable, or toxic cell material using protease enzymes present within membrane-bound organelles\(^11\). Autophagic clearance pathways may have many variants that select and degrade cellular proteins and debris differentially through varying mechanisms using multiple selections and targeting mechanisms using several adapters and membrane-bound receptor proteins\(^35,229\). In a way, this leads to a variety of opportunities to regulate these pathways of degradation at various points. An array of reports has shown that autophagy regulation using small natural molecules could also be achieved and used for drug discovery purposes\(^229,230\). Modulation of autophagic pathways is proposed for therapies against cancer and neurodegeneration in a large number of studies\(^231,232\). As shown in Table 4, different types of proteinopathies, neurogenerative disorders, cancers, and several systemic diseases could be targeted by derivatives of natural molecules with modulatory effects on various effectors of the autophagy pathway. Several reports could still not be included in the present article due to space restrictions. The most prominent members of this class of natural autophagy inducers are resveratrol and trehalose\(^33,234\). Both these inducers have shown the tremendous potential of relieving neurons from various stresses by reducing free radicals and degrading protein aggregates\(^234,235\).

Interestingly, autophagy plays very crucial roles in the clearance of many infectious agents, including HIV, *Mycobacterium*, or other parasites\(^236\). Triggering this pathway by vitamin D or starvation mechanisms have shown improvements in various pathological conditions, ranging from viral/bacterial infections to tuberculosis and malaria\(^237-240\). Autophagy also performs vital roles in cell metabolism and signaling, as evidenced by multiple lines of studies, which are covered in detail in several previous articles\(^231,232\). The influence of autophagy induction has been investigated in many metabolism-related disorders, including diabetes, glucose intolerance, obesity, and atherosclerosis\(^15\). It was evident from the past studies that modulation of autophagy may have enormous potential to counter the stress conditions and protect from several incurable diseases\(^243-245\). Likewise, the autophagy inducers, e.g., bigelovin, oridonin, and stellettin B may accelerate the apoptotic pathways in various types of cancer cells\(^246-248\). The majority of molecules (e.g., cinobufagin,
juglanin, ursolic acid, amelopsin, etc.) act on the target proteins, like PI3K, AKT, mTOR, S6K, MAPK, JNK, P38, ERK, etc., which are explicitly involved in the autophagy regulation. For the past many decades attempts to upregulate the autophagic degradation of large aggregates of proteins have been made, and considerable success has been achieved. The research on exogenous autophagy induction using exercise/starvation like lifestyle changes or natural molecule-based food habits has shown enormous promises to deliver in many stress-related changes like neurodegeneration and aging. Use of curcumin and triptolide in oxidative stress conditions in cells and Parkinson’s disease animal models have shown neuroprotective effects of these drugs via the upregulation of autophagy. Docosahexaenoic acid, sulforaphane, and lanosterol are other natural inducers of autophagy, which have shown multifactorial effects in ameliorating the stress conditions of the cells and alleviate the degenerative conditions in the brain. Although a vast literature is available on the induction of autophagy by small molecules, there are limited reports of inhibitors that can demonstrate beneficial effects on disease conditions. Emodin, wortmanin, and 3-methyladenine are few known autophagy suppressors with disease modulating potential. A comprehensive list of naturally derived inducers and inhibitors of the autophagy pathway is prepared in Table 4.
5. Conclusions and future perspectives

Aberrant protein’s accumulation inside cells is very well-described as a leading factor of aging, neurodegeneration, and multiple other pathologies, including cancer, diabetes, cystic fibrosis, etc. Researchers and clinicians have made multiple efforts to understand the underlying causes and mechanisms for these diseases. The molecular mechanisms whose failures can lead to inappropriate protein folding events and the common features across all these pathologies are still unclear. Some unique features across all these diseases and a noticeable genetic diversity in various conditions have prevented the scientific community from reaching a common conclusion and devising possible solutions for these life-threatening diseases.35,261 However, continuous efforts are made worldwide to identify underlying causes, including the most common genetic mutations and contributing environmental or lifestyle-associated factors. A comprehensive picture of all these factors, associated changes, and the pathological conditions caused by them is presented in Fig. 3. Unfortunately, none of the hypotheses and explanations addressing the mechanisms and causes behind such detrimental changes leading to the age-associated decline in the efficiency of physiological systems have led us to develop a proper understanding and possible solutions to these conditions.

In the past, many attempts, both successful and unsuccessful, have been made for devising novel therapeutic approaches against various diseases. Numerous molecules have been proposed for their efficacy for mitigating the proteotoxicity generated by intracellular protein aggregates or inclusion bodies.106,110,111 One consensus that most of the studies meet is that natural products could be medicinally very active and useful. They were used for centuries in ancient traditional natural medicinal approaches in old-world countries. Based on all the observations mentioned above, it could be stated that targeting cellular PQC machinery by modulating their activities using small molecules may have vast potential. Plant extracts were used by ancient researchers and physicians to cure deadly infections and diseases, described in many primitive Indian, Unani, and Chinese literature.262,263 Most natural molecules posit lesser toxicity and side effects than synthetic chemicals when administered to cells or animals in laboratory tests.264 This makes them preferred choices over costly synthetic chemicals in experimental studies. Many less-invaded human territories, like the Himalayas, are the homeland of such medicinally rich natural resources and are yet to be explored and utilized for treatments of life-threatening diseases in these regions. A thorough and well-managed exploration could be done in order to identify and delve into more effective and easily derived drugs.

Several naturally extracted drugs obtained from microbial and fungal isolates, marine and land animals, many aquatic and terrestrial plants, are currently in research allowing us to identify and investigate more such drugs. These small natural molecules may have several unexplored applications that need further studies. The primary benefit of these naturally derived molecules is a low-cost therapeutic alternative to many treatment strategies, which are in the pipeline against these diseases and may need a much higher cost, although many challenges remain unaddressed.19,206 The identification, isolation, purification, and characterization of new molecules are a highly tedious and lengthy process, requiring lots of hard work, funds, and time.19,206 Many times, designing or synthesizing some derivatives of already known drugs seems a more straightforward and cost-effective strategy in comparison to looking for new molecules.

Repurposing older drugs could also be a beneficial drug discovery model to save much time, effort, and cost. Additionally, these small plant-based molecules could be used as food supplements to reduce the overall risk of many diseases.

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Author contributions

Arun Upadhyay is responsible for all work of this review.

Conflicts of interest

The author has no conflict of interest to declare.

Supporting information

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