# Autophagy Induction: Host-Directed Therapeutic Strategy

Subjects: Pathology

Contributor: Sivakumar Shanmugam, Radha Gopalaswamy

Tuberculosis (TB), a bacterial infectious disease caused by Mycobacterium tuberculosis (M.tb), causes significant mortality in humans worldwide. The current treatment regimen involves the administration of multiple antibiotics over the course of several months that contributes to patient non-compliance leading to relapse and the development of drug-resistant M.tb (MDR and XDR) strains. Together, these facts highlight the need for the development of shorter TB treatment regimens. Host-directed therapy (HDT) is a new and emerging concept that aims to augment host immune response using drugs/compounds with or without adjunct antibiotics against M.tb infection. Autophagy is a natural catabolic mechanism of the cell that involves delivering the cytosolic constituents to the lysosomes for degradation and recycling the components; thereby maintaining the cellular and energy homeostasis of a cell. However, over the past decade, an improved understanding of the role of autophagy in immunity has led to autophagy activation by using drugs or agents. This autophagy manipulation may represent a promising host-directed therapeutic strategy for human TB.

Keywords: Mycobacterium tuberculosis ; host-directed therapies ; autophagy ; adjuvants

## 1. Introduction

Tuberculosis (TB) disease continues to be a global health threat with high morbidity and mortality, particularly in developing countries [1]. TB is primarily caused by *Mycobacterium tuberculosis* (*M.tb*), a successful intracellular pathogen that invades human lungs as droplet nuclei [2]. Despite the directly observed treatment short-course (DOTS) program, the incidence of TB is exacerbated by co-infections, co-morbidities, the emergence of drug-resistant (DR) *M.tb* strains, and a rise in the reservoir of latent *M.tb* infection (LTBI) [3]. The current anti-TB therapy has many limitations including long duration, use of multiple antibiotics, adverse effects of drugs, and an associated lack of patient compliance. These limitations highlight the need to develop new treatment and management strategies for both drug-sensitive (DS) and drug-resistant (DR) TB in order to control infection more effectively [4]. The host immune status plays a significant role in TB disease outcome, though *M.tb* possesses several evasion strategies that favor its persistence and survival [5]. Thus, using adjunctive treatments with host-directed therapeutic (HDT) drugs that can modulate the host immune response is a promising strategy to increase the success of TB treatment [4]. Many studies have suggested that autophagy plays a key role in modulating host innate immune response by promoting several critical elements that target and eliminate intracellular pathogens [6][7][8]. Given these observations, the use of HDT drugs to upregulate autophagic pathways is currently receiving considerable attention as it could lead to effective treatment alternatives for both DS and DR TB. In this regard, repurposed compounds with prior safety and regulatory approval that could potentially target autophagy are mostly investigated for further approval as HDT drugs in TB treatment [3].

## 2. Potential Autophagy Activating Drugs for Host Directed Therapy against Mycobacterial Infection in Pre-Clinical Trials

Host-directed therapeutic strategy that enhances the protective immunity against emerging infectious diseases has gained significant importance over the last two decades [9]. Host-directed therapeutic drugs as adjuncts with existing TB drugs for *M.tb* infection could lead to shorter and more effective treatments for tuberculosis. A literary search of pre-clinical trials and animal model studies revealed that repurposing licensed drugs with autophagy inducing potential, showed effective therapeutic manipulation of host immunity against *M.tb* infection. Many of these drugs already have well-defined safety and pharmacokinetic profiles and are more likely to be investigated in randomized and controlled clinical trials that will evaluate their effectiveness in TB. The potential HDT drug candidates from different drug/compound types that target

autophagy and the mechanism involved in manipulating host immunity against *M.tb* infection are summarized in Figure 1 and Table 1.

**Table 1.** List of potential host-directed therapeutic agents targeting autophagy and their mechanism to aid antimycobacterial host defense.

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| **Small Molecules** | | | | | |
| SMER | SMER18 and 28 | - | Induced autophagosome formation | Human PBMCs | [10] |
| Analog of AMP | AICAR | Allosteric activation of AMPK kinase which plays a key function in cellular homeostasis | Activates AMPK-PPARGC1A pathway that upregulates CEBPB-dependent autophagy genes and enhances autophagy. | RAW264.7 cells, THP-1 cells (human monocytic cell line), BMDMs, mice and *Drosophila* | [11] |
| Synthetic small molecule | GSK4112 | Activates NR1D1 receptor | Increases autophagic flux via upregulation of TFEB signaling | THP-1 cells, primary human monocyte, murine macrophage cell line, RAW264.7, HEK293T and HepG2 cell lines. | [12] |
| | GW7647 | Activates PPARα receptor | Increases autophagic flux via upregulation of TFEB signaling, and enhanced lipid catabolism | BMDMs | [13] |
| | SRT 1720 | SIRT 1 activator | Enhances autophagy by activating SIRT 1 | THP-1 cells, HMDMs and mice | [14] |
| | NSC 18725 | Anti-mycobacterial activity | Modulates autophagy, mechanism unknown | THP-1 cells | [15] |
| Amino acid | Gamma amino Butyric acid | Neurotransmitter inhibitor | Increases autophagic flux via $Ca^{2+}$-AMPK signaling pathway. Additionally, increases phagosomal maturation | Human PBMCs, HMDMs, RAW264.7 cells and BMDMs | [16] |
| | Ornithine | Crucial role in disposing of excess nitrogen (ammonia) via the urea cycle | Increases autophagy by reducing ammonia levels thereby upregulating AMPK phosphorylation | Mouse alveolar macrophage, peritoneal macrophages, kupffer cells and BMDMs | [17] |

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| Disaccharides | Trehalose | - | Induces autophagic flux by increasing PI(3,5)P2 levels that activate calcineurin triggered translocation of TFEB. Additionally, it causes a pseudo-starvation like a response by inhibiting glucose transporters (GLUT 3 and 8) to induce autophagy | U937, U1.1 and HEK293T cell lines | [18] |
| Immunosuppressants | | | | | |
| Macrolide compound | Rapamycin | Forms an immunosuppressive complex by binding to the immunophilin and also a potent mTOR inhibitor | Autophagy induction via mTORC1 complex inhibitor | Raw264.7 cells, HMDMs, Human PBMCs and BMDMs | [6] |
| Rapamycin analog | Everolimus * | Inhibits the activation of mTOR by forming a complex with FKBP-12 protein | Autophagy induction via mTORC1 complex inhibitor | - | [19] |
| Immunomodulators | | | | | |
| Vitamin | Vitamin D * | Regulation of hormone secretion, cell proliferation, differentiation and immune response | Induces autophagic flux via a signaling cascade that is triggered by the induced expression of human cathelicidin (hCAP-18/LL-37) | Primary human monocytes, HMDMs, THP-1 cells and RAW 264.7 cells | [20][21] |
| Cytokine | Interferon-γ (IFN-γ) | Promotes macrophage activation | Activates autophagic flux through vitamin D dependent effector pathway | Human T cells, primary human monocytes and HMDMs | [22] |
| Nucleoside analog of imidazoquinoline, a synthetic tricyclic organic molecule | Imiquimod | TLR7 and 8 agonist | Induces Autophagy by increasing mitochondrial ROS that triggers selective autophagy. Additionally, upregulates NO Production via the MEK/ERK1/2 and GSK-3β mediated Pathways. | Raw264.7 cells and THP-1 cells | [23] |
| Endotoxin derived from the outer membrane of Gram-negative bacteria | Lipopolysaccharides (LPS) | TLR4 agonist | Activates autophagy and restores *M.tb* inhibited immune activity | THP-1 cells | [24] |
| Plant compounds | | | | | |
| Stilbene | Resveratrol | SIRT 1 activator | Enhances autophagy by activating SIRT 1 | THP-1 cells, HMDMs and mice | [14] |

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| Flavone glycoside | Baicalin | - | Induces the activation of autophagy by inhibiting PI3K/Akt/mTOR pathway. Additionally, inhibits the PI3K/Akt/NF-kB signal pathway, thereby limiting the NLRP3 inflammasome and subsequent production of pro-inflammatory cytokine IL-1β | Mice, raw264.7 cells, murine macrophage | [25] |
| Eurycomanone | Pasakbumin A | - | Induces autophagic flux and TNF-α production via activation of the ERK1/2-signaling pathway and enhances phagosome maturation and lysosome fusion | Raw264.7 cells, and THP-1 cells | [26] |
| Polyphenolic compound | Epigallocatechin gallate | - | Induces autophagic flux | Raw264.7 cells and mice | [27] |
| Lignans (low molecular weight polyphenols) | Honokiol | SIRT 3 activator | Increases autophagic flux via upregulation of TFEB signaling | Mice, BMDMs, HMDMs and Human PBMCs | [28] |
| Legume Lectins | Soybean lectin | - | Induces autophagic flux by activating P2RX7 that triggers $Ca^{2+}$/AMPK signaling pathway and ROS generation via P2RX7/NF-κB axis | THP-1 cells | [29] |
| | | Antibiotics | | | |
| Small molecule–Isonicotinic acid derivative | Isoniazid | Inhibits the enzyme inh A during mycolic acid synthesis | Induces autophagic flux via NOX- derived ROS and calcium, $Ca^{2+}$ and AMPK dependent pathways | BMDMs and HMDMs | [30] |
| Small molecule—Nicotinamide analogue | Pyrazinamide | Disrupts membrane potential, interferes with energy production and inhibits trans-translation by binding to ribosomal protein S1 | Induces autophagic flux via NOX- derived ROS and calcium, $Ca^{2+}$—dependent AMPK activation | BMDMs and HMDMs | [30] |
| Thiopeptide | Thiostrepton | Disrupts prokaryotic translation by inhibiting the dissociation of elongation factor G from ribosomes | ER stress-mediated autophagy activation | Zebrafish and Raw264.7 cells | [31] |
| Polyether | Calcimycin | Forms stable complexes with divalent cations and helps in membrane transportation | Induces autophagic flux by activating P2RX7 that triggers $Ca^{2+}$/AMPK signaling pathway and IL-12 generation via P2RX7/NF-κB axis | THP-1 cells | [32][33] |
| | | Steroids | | | |

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| Hormones | Dehydroepiandrosterone | Inhibits voltage-gated T-type calcium channels and activates PPARα | Induction of autophagy | THP-1 cells | [34] |
| Anticancer drugs | | | | | |
| Signal transduction inhibitor | Gefitinib | EGFR inhibitor | Enhancing host autophagy by inhibiting EGFR-mediated phosphorylation of the downstream signaling molecule p38 MAPK. Depletion of p38 MAPK activates autophagy via p38IP and mATG9 | J774 macrophages and BMDMs | [35] |
| Histone deacetylase inhibitor | 4-phenylbutyrate * | Transcription activation via acetylation of histones | LL-37-mediated autophagy activation via P2RX7 receptor which in turn activates AMPK and PI3K downstream of the P2RX7 receptor together with enhanced cytosolic free $Ca2^{+}$ | HMDMs, and THP-1 cells | [36] |
| Kinase inhibitor | Imatinib * | Tyrosine kinase inhibitor | Increases autophagic flux by activating cathepsin D and increasing phagolysosomal acidification via the inhibition of ABL tyrosine kinase | Human PBMCs, HMDMs, human alveolar macrophages | [37] |
| | Nilotinib | Tyrosine kinase inhibitor | Promotes autophagy by inhibiting the ABL tyrosine kinase-mediated PI3K/Akt/mTOR pathway | THP-1 cells, RAW264.7 cells and BMDMs | [38] |
| | Ibrutinib | Bruton's tyrosine kinase (BTK) inhibitor | Induces autophagy through inhibition of BTK/Akt/mTOR pathway and also facilitates the completion of autophagic flux | THP-1 cells | [39] |
| Estrogen agonists | Bazedoxifene | Selective estrogen receptor modulator | Enhances autophagosome formation via phosphorylation of Akt/mTOR signaling | THP-1 cells | [40] |
| Antidiabetic drugs | | | | | |
| Biguanides | Metformin * | Activates AMPK via inhibiting mitochondrial respiratory complex I which elevates 5'-adenosine monophosphate (AMP) levels | Increases autophagic flux via enhancing autophagosome—lysosome fusion and additionally increases mROS production | THP-1 cells, HMDMs and mice | [41] |
| Antidiarrheal drugs | | | | | |

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| Synthetic opioid — phenylpiperidine derivative | Loperamide | Decreases peristaltic activity by binding to opiate receptors in the gastrointestinal tract, blocks voltage-dependent calcium channel and calmodulin inhibitor | Increased autophagy induction by upregulating the expression of genes viz., ATG16L1 and LC3 | Mice, HMDMs, murine alveolar cells and Human alveolar macrophages | [42] |
| Antiprotozoal agents | | | | | |
| Antiprotozoals | Nitazoxanide | Inhibits pyruvate: ferredoxin oxidoreductase enzyme-dependent electron transport and disrupts metabolism in anaerobic microbes | Autophagy induction via mTORC1 complex inhibitor | THP-1 cells, MCF-7 cells, HEK 293T cells and MEF cells | [43] |
| Antiseizure drugs | | | | | |
| First-generation (classic) anticonvulsants | Carbamazepine | Inactivates Na+ channels and inhibits receptors of CNS | Induction of mTOR-independent autophagy through Ins(1,4,5)P3depletion and AMPK activation | RAW264.7 cells, HMDMs, human alveolar macrophages, zebrafish and mice | [44] |
| | Valproic acid | Inhibits GABA transaminase and increases GABA levels in CNS. It also inhibits histone deacetylase | Induction of mTOR-independent autophagosome formation through ATG12 | RAW264.7 cells, HMDMs and human alveolar macrophages | [44] |
| Lipid-lowering drugs | | | | | |
| Fibrate | Wy14643 | Activates PPARα receptor protein | Increases autophagic flux via upregulation of TFEB signaling, and enhanced lipid catabolism | Mice and BMDMs | [13] |
| Statins | Pravastatin *, Rosuvastatin *, Atorvastatin * and Simvastatin | HMG-CoA reductase inhibitors | Promotes autophagy via the AMPK/mTORC1/TFEB axis. Additionally increases phagosome maturation and lysosome fusion | Human PBMCs, HMDMs, THP-1 cells and mice | [45][46][47] [48] |
| Mucoactive drug | | | | | |
| Mucokinetics | Ambroxol | Suppresses excessive mucus secretion by inhibiting NO-dependent activation of soluble guanylate cyclase | Induction of autophagy via, the activation of TFEB nuclear translocation | Mice and BMDMs | [49] |
| Psychotropic Drugs | | | | | |
| Anti-depressant | Nortriptyline | Norephinephrine and sereotonin reuptake inhibitor | Induces the formation of autophagosomes | HeLa cells and HMDMs | [50] |

| Class | Drugs/Compounds | Drug Action | Mechanism of Autophagy Activation during Mycobacterial Infection | Model | Reference |
|---|---|---|---|---|---|
| | Fluoxetine | Sereotonin reuptake inhibitor | Induces autophagy by increasing the secretion of TNF- α | THP-1 cells, RAW264.7 cells, J774 macrophages and BMDMs | [35] |
| Antipsychotics | Prochlorperazine edisylate | D2 dopamine receptor inhibitor | Slows down autophagic flux and progressively increases the acidity of lysozymes | HeLa cells and HMDMs | [50] |

### 4.1. Small-Molecules

Small molecules are increasingly being tested for their ability to enhance autophagy against different disease phenotypes [51]. Many small-molecules have also been reported for their ability to inhibit intracellular *M.tb* replication through autophagy activation [10][11][12][13][14][15][16][17][18]. Flotoet al. described two compounds termed small-molecule enhancers of rapamycin (SMERs) that induce autophagy at the stage of autophagosome formation without decreasing mTOR activity. The SMER 18 and 28 had the highest autophagic activity in *M.tb* infected human peripheral blood mononuclear cells (PBMC), resulting in the inhibition and clearance of intracellular *M.tb* [10].

The small molecule 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), a direct AMPK activator, was reported to enhance autophagy in different mammalian cells viz., human monocytic cell line (THP-1 cells), RAW 264.7 cells and mice bone marrow derived macrophages (BMDMs) against *M. bovis* BCG and *M. tuberculosis* strain H37Rv [11]. This molecule induces autophagy in *M.tb* infected cells by activating AMPK that inhibits *M.tb*-mediated mTOR activation. Furthermore, this AMPK activation by AICAR induced Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A), a transcriptional coactivator protein that upregulated multiple autophagy related genes via CCAAT/enhancer-binding protein β (CEBPB) and enhanced autophagic flux in *M.tb* infected cells [11].

The synthetic small molecule, GSK4112 that acts as an agonist to nuclear receptor subfamily 1, group D, member 1 (NR1D1), a transcriptional repressor protein was reported to induce autophagic flux and increase lysosome biogenesis [12]. The transcriptional protein NR1D1 plays a key role in infection and inflammation [52] and its activation led to the modulation in the expression of transcription factor EB (TFEB). The upregulation of TFEB increased the number of both autophagosomes and lysosomes in *M. tuberculosis* strain H37Rv infected THP-1 cells [12].

Kim et al. reported that GW7647, a synthetic small molecule agonist of the PPARα transcription factor enhances autophagic flux against *M. bovis* BCG and *M. tuberculosis* strain H37Rv in mice BMDMs. The PPARα activation by GW7647 resulted in the upregulation and translocation of TFEB, a critical regulator of various genes involved in autophagic flux. Further, PPAR-α activation inhibited lipid body formation during mycobacterial infection [13].

The small molecule SRT 1720, a synthetic activator of sirtuin 1 (SIRT1) deacetylase was observed to restrict the growth of intracellular mycobacteria in THP-1 cells and human primary monocyte-derived macrophages(HMDMs) [14]. The SIRT1 mainly regulates cellular homeostasis, and its activity depends on the availability of intracellular nicotinamide adenine dinucleotide (NAD+) [53]. Cheng et al. reported that the *M.tb* infection reduced the intracellular NAD+/NADH ratio resulting in the down-regulation of SIRT1 expression. This was reversed by the addition of SRT 1720 and in addition, the SRT 1720 mediated SIRT1 activation in mycobacteria infected cells induced autophagy and phagosome-lysosome fusion [14].

The small molecule NSC 18725, a pyrazole derivative was reported to inhibit intracellular *M.tb* growth by inducing autophagy in differentiated THP-1 macrophages [15].

The amino acid Gamma-aminobutyric acid (GABA), a potent neurotransmitter inhibitor, was linked to autophagy activation and host protection against intracellular mycobacterial infections [16]. Autophagy was promoted in macrophages on treatment with GABA. The GABAergic treatment in *M.tb* infected macrophages triggered the increase in intracellular $Ca^{2+}$ levels and phosphorylation of AMPK, resulting in autophagic activation. Further, GABAergic activation increased the expression of GABARAPL1, a key autophagy-associated protein required for phagosomal maturation [16].

Mouse alveolar macrophages (AMs) supplemented with amino acid ornithine was reported to enhance autophagy resulting in increased *M.tb* clearance [17]. Generally, ornithine plays a crucial role in disposing of ammonia produced in

cells through deamination of amino acids via urea cycle [17]. Mycobacteria also produce and utilize ammonia as a source of nitrogen for its metabolic activity in infected macrophages [54]. Therefore ornithine supplementation in *M.tb* infected AMs reduced ammonia levels and additionally upregulated AMPK phosphorylation which inhibits mTOR resulting in autophagy activation [17].

Trehalose, a naturally occurring disaccharide was reported to facilitate autophagy in different cell lines (U937, U1.1 and HEK293T) against *M.tb* and non-tuberculous mycobacterial (NTMs) strains either alone or during co-infection with HIV-1 [18]. This disaccharide small molecule induced autophagic flux by increasing phosphatidylinositol 3,5-bisphosphate (PtdIns(3,5)P2) that served asmucolipin subfamily, member 1(MCOLN1) channel agonist and increased $Ca^{2+}$ release from lysosomal lumen [55]. The released $Ca^{2+}$ activates calcineurin, a serine-threonine phosphatase that dephosphorylates TFEB, resulting in trehalose mediated nuclear translocation of TFEB and mTOR independent autophagy activation in macrophages [18]. Additionally, trehalose caused a pseudo-starvation like a response by competitively inhibiting GLUT transporters viz., SLC2A3/GLUT3 and SLC2A8/GLUT8, resulting in autophagy induction via mTOR inhibition and AMPK activation [18].

### 2.2. Immunosuppressants

Rapamycin a macrolide immunosuppressive compound and its analog everolimus were reported to enhance autophagy through mTOR inhibition and concomitantly suppress the growth of intracellular *M.tb* and *M. bovis* BCG strains in different cells [6][19].

### 2.3. Immunomodulators

Vitamin D plays an important role as an immunomodulator in strengthening the innate immune system to fight against pathogens [56]. In addition, vitamin D was reported to enhance autophagic flux in macrophages and restrict the growth of intracellular *M.tb* [20][21]. The active form of vitamin D that is 1,25-dihydroxyvitamin D3 (1,25D3) increased autophagic flux by inducing the gene expression of human antimicrobial protein, cathelicidin (hCAP-18/LL-37) which in turn triggers MAPKs and C/EBP β-binding sites, resulting in transcriptional activation of Beclin-1 and ATG5. Vitamin D also promoted cathelicidin recruitment into *M.tb* containing autophagosome through calcium/calmodulin dependent protein kinase-β (CAMKK-β) and AMPK dependent pathways in infected macrophages [20][21]. The cytokine interferon-γ (IFN-γ) was studied for its ability to induce autophagic flux and inhibit intracellular *M.tb* in different cells viz., human T cells, primary human monocytes and HMDMs.

The IFN- γ mediated activation of autophagic flux in *M.tb* infected cells was dependent on vitamin D sufficiency [22].

Imiquimod, a nucleoside analog of imidazoquinoline that stimulates TLR7 was reported to enhance autophagy and control *M.tb* infection in Raw264.7 cells and THP-1 cells. The imiquimod mediated autophagy activation was associated with induced oxidative stress, triggered by mitochondrial reactive oxygen species (ROS) production that activates selective autophagy (mitophagy) by enhancing interaction between Beclin-1 and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), resulting in intracellular *M.tb* elimination in infected macrophages. Further, imiquimod also upregulated the nitric oxide (NO) production by the mitogen activated protein kinase/extracellular-signal-regulated kinase 1/2 (MEK/ERK1/2) and glycogen synthase kinase 3 β (GSK-3β) signaling pathways that lead to autophagy induction [23].

Lipopolysaccharides (LPS), an endotoxin derived from the outer membrane of gram-negative bacteria that functions as a TLR 4 agonist was reported to induce autophagy as evidenced by the significant rise in protein expression in *M.tb* infected THP-1 cells [24].

### 2.4. Plant Compounds

Many plant compounds have been studied for their ability to induce autophagy against *M.tb* infection [14][25][26]. Resveratrol, a stilbene derivative, was reported to activate SIRT1 deacetylase that lead to the induction of autophagy and phagosome-lysosome fusion in *M.tb* infected THP-1 and HMDMs cells [14].

Baicalin, a flavone glycoside, induced autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway in *M.tb* infected macrophages. Additionally, baicalin-mediated autophagy activation inhibited *M.tb* infection caused nuclear factor kappa B (NF-kB) signaling, NLR family pyrin domain containing 3 (NLRP3) inflammasome activity and the production of pro-inflammatory cytokine IL-1b [25].

Pasakbumin A, a eurycomanone compound isolated from *Eurycoma longifolia,* restricted the growth of *M.tb* strain H37Rv in different cells such as Raw264.7, and THP-1 cells [26]. This compound activated both autophagy and tumour necrosis

factor alpha (TNF-α) production through the ERK1/2-mediated signaling pathway. Further, pasakbumin A induced phagosomal maturation in *M.tb* infected macrophages [26].

Epigallocatechin-3-gallate (EGCG), a major polyphenolic compound found in green tea extract, was reported to enhance autophagic flux and suppress intracellular growth of *M.tb* in Raw264.7 cells and mice [27].

Honokiol, a low molecular weight polyphenols that activates sirtuin 3 (SIRT3) deacetylase, was reported to promote autophagic functions in different macrophages viz., BMDMs, HMDMs and human peripheral blood mononuclear cells (PBMCs) against *M. bovis* BCG and *M.tb* H37Rv strains [28]. The honokiol-mediated autophagy activated SIRT3, which consecutively triggered the expression of PPARα transcription factor resulting in the upregulation and translocation of TFEB, a critical regulator of various genes involved in autophagic flux [28].

Soybean lectin (SBL) isolated from soybean (*Glycine max*) seeds was reported to induce autophagy and curtail intracellular growth of *M. smegmatis* $mc^2$ 155 and *M. bovis* BCG in THP-1 cells [29]. The SBL activated P2RX7 receptor that triggered the downstream activation of $Ca^{2+}$—AMPK signaling pathway. Further, the activated P2RX7 triggered ROS generation via NF-κB activation and nuclear translocation, resulting in autophagic flux activation [29].

**2.5. Antibiotics**

Antimycobacterial drugs, viz., isoniazid (INH) and pyrazinamide (PZA), were studied for their ability to activate autophagy in human and murine macrophages against *M.tb* infection. The antibiotic induced autophagy was triggered by the increased mitochondrial ROS production via the enzyme NADPH oxidase 2 (NOX2). In addition, these antibiotics induce intracellular calcium influx that triggers $Ca^{2+}$ dependent autophagy through the downstream phosphorylation of AMPK [30].

Thiostrepton, a thiopeptide antibiotic, was reported to induce autophagy in *M. marinum*infected RAW264.7 cells and a zebrafish model. This antibiotic inhibits proteasomes that leads to an increase in unfolded/misfolded proteins resulting in ER stress, followed by selective autophagy activation as a defense mechanism for cell survival [31].

Calcimycin, a polyether antibiotic from *Streptomyces chartreusensis*, was reported to kill intracellular mycobacteria by inducing autophagy in infected THP-1 cells. This drug binds to P2RX7 receptor and induces autophagy by triggering the upregulation of intracellular $Ca^{2+}$ levels, resulting in AMPK phosphorylation and increasing interleukin—12 (IL-12) production via NF-κB activation [32][33].

**2.6. Steroids**

Dehydroepiandrosterone (DHEA) is a steroid hormone that activates PPARα and enhances autophagic flux in THP-1 cells infected with *M. tuberculosis* [34].

**2.7. Anti-Cancer Drugs**

Anti-cancer drugs are used to either destroy or slow the growth of cancer cells. These drugs are given with a curative intent or as a palliative therapy that aims to reduce symptoms and prolong life [57]. Apart from cancer treatment, some anticancer drugs were also evaluated for their ability to induce autophagy [35][36][37][38][39][40]. Stanley et al. reported that gefitinib, a signal transduction inhibitor that inhibits epidermal growth factor receptor (EGFR) induces autophagy in a number of cell lines including THP-1 cells, RAW 264.7 cells, and J774A.1 cells against *M.tb* strain H37Rv. This drug restricts *M. tuberculosis* growth in cells by depleting p38 mitogen activated protein kinase (p38 MAPK) molecules in EGFR/p38 MAPK signaling pathway. As p38 MAPK acts as a negative regulator of autophagy, its depletion activates autophagy viap38-interacting protein(p38IP) and mATG9 [35].

In another study, 4-phenylbutyrate (PBA), a histone deacetylase inhibitor that activates transcription activation via acetylation of histones, was reported to induce autophagy in HMDMs and THP-1 cells against *M.tb* strain H37Rv [36]. This drug induced the expression of the antimicrobial peptide LL-37 that activates an mTOR-independent autophagic pathway via the purinergic receptor P2RX7 which signals the downstream activation of AMPK and PI3K in the presence of intracellular $Ca^{2+}$ [36].

Imatinib, a tyrosine kinase inhibitor that increases autophagic flux by activating cathepsin D and phagolysosomal acidification, results in the inhibition of intracellular *M.tb* infection in human macrophages [37]. Nilotinib, a tyrosine kinase inhibitor, was identified to regulate autophagy and inhibit *M. bovis* and *M. avium* subspecies *paratuberculosis* (MAP) in different cells such as THP-1 cells, RAW264.7 cells and BMDMs. Nilotinib inhibits the phosphorylation of PI3k/Akt/mTOR signalling by blockingabelson tyrosine kinase (c-ABL) in mycobacteria infected macrophages [38]. Hu et al. [39] reported that the drug ibrutinib, which inhibits Bruton's tyrosine kinase (BTK) suppresses intracellular *M.tb* growth by inducing

autophagy in THP-1 cells via inhibition of BTK/Akt/mTOR pathway. By inhibiting BTK, ibrutinib blocks the downstream signaling molecule protein kinase Cβ (PKC β) which is an essential regulator of Akt/mTOR signaling pathway that suppresses autophagy [58]. Additionally, ibrutinib also facilitates the completion of autophagic flux that degrades intracellular *M.tb* in autolysosome compartments [39]. Bazedoxifene, a newer selective estrogen receptor modulator was reported to inhibit *M.tb* growth significantly in THP-1 cells by inducing autophagy. This drug increases mROS production and promotes autophagosome formation via phosphorylation of Akt/mTOR signaling [40].

### 2.8. Anti-Diabetic Drugs

Anti-diabetic drugs are used in the treatment of type 2 diabetes mellitus, a metabolic condition mainly characterized by hyperglycemia [59]. Metformin is an antidiabetic drug of the biguanide class that functions by inhibiting mitochondrial complex I which leads to increased cytoplasmic ADP:ATP and AMP:ATP ratios and the activation of AMPK enzyme [60]. This drug was reported to restrict the growth of intracellular BCG as well as the H37Rv strain of *M.tb* in THP-1 cells and HMDMs by enhancing autophagic flux [41].

### 2.9. Anti-Diarrheal Drugs

Antidiarrheal drugs are used to treat acute or chronic diarrhea by binding to opiate receptors in the gastrointestinal tract, resulting in decreased peristaltic activity [61]. Loperamide, a synthetic opioid–phenylpiperidine derivative commonly used for the treatment of diarrhea, was reported to restrict intracellular growth of *M. tuberculosis* in different macrophages viz., murine alveolar macrophages, human alveolar macrophages and HMDMs. This drug induced autophagy in *M.tb* infected macrophages by increasing the upregulation of ATG16L1 and LC3 gene expression and the induced autophagy pathway was completed as evidenced by autophagic substrate p62 degradation [42].

### 2.10. Anti-Protozoal Drug

Nitazoxanide, a thiazolide class of antiprotozoal drug, stimulates autophagy and inhibits intracellular *M. tuberculosis* proliferation in different cell lines such as THP-1, Michigan cancer foundation-7 (MCF-7), human embryonic kidney cells(HEK) 293T and mouse embryo fibroblasts (MEF) cells [43]. This drug inhibited human quinone oxidoreductase NQO1, a scavenger for a broad range of reactive substrates including the ROS. The authors speculate that NQO1 inhibition by nitazoxanide may increase oxidative stress, resulting in mTORC1 inhibition and autophagy activation, thereby inhibiting intracellular *M.tb* proliferation [43].

### 2.11. Anti-Seizure Drugs

Anti-seizure drugs are generally prescribed to patients with epilepsy, a condition that causes recurrent seizures [62]. Additionally, antiseizure drugs from anticonvulsant class are also used for the treatment of several non-epileptic neurological conditions and psychiatric disorders [63]. Some of the first-generation classic anticonvulsants viz., carbamazepine and valproic acid were studied for their ability to induce autophagy [44]. Carbamazepine, a sodium channel blocker that binds and inactivates voltage-gated sodium channels, which inhibits receptors of the central nervous system (CNS). Schiebleret al. reported that carbamazepine induces antimicrobial autophagy against *M. bovis* BCG and *M.tb* strain H37Rv in both mammalian cells and animal models. This drug induces AMPK activation of autophagy by an mTOR-independent pathway, which is controlled by cellular depletion of myo-inositol levels [44]. Schiebleret al. also worked with valproic acid, a drug that inhibits GABA transaminase and increases GABA levels in CNS. This drug induces mTOR-independent autophagy by increasing the rate of autophagosome formation in *M.tb* infected cells [44].

### 2.12. Lipid Lowering Drugs

Lipid lowering drugs are used in the treatment of hyperlipidemia that functions by decreasing the production and increasing the degradation of cholesterol levels [64]. Nonetheless, some drugs from the group fibrates and statins were evaluated for their ability to induce autophagy [13][45][46][47][48]. The fibrate Wy14643 enhanced autophagic flux in *M.tb* infected mice BMDMs by inducing the transcription factor PPARα, resulting in the upregulation and nuclear translocation of TFEB [13]. Alternatively, statins are also a group of lipid lowering drugs used in the treatment of hypercholesterolemia, which functions by inhibitingβ-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase [64]. Studies have reported that statins such as simvastatin, rosuvastatin and atorvastatin enhanced autophagy and phagosomal maturation in different cells viz., against *M. leprae*, *M. bovis* and *M.tb* infection [45][46][47][48]. Statins decrease cholesterol levels and alter cellular AMP:ATP ratios in *M.tb* infected macrophages, resulting in the activation of autophagy via AMPK-mTORC1-TFEB axis. Further, the statin mediated decrease in intracellular cholesterol levels had induced phagosomal maturation and lysosomal fusion in *M.tb* infected macrophages [45].

### 2.13. Mucoactive Drugs

Mucoactive drugs are used to treat mucus hypersecretion, a clinical complication in respiratory diseases [65]. Ambroxol, a mucokinetic drug that suppresses excessive mucus secretion, was described to enhance autophagic flux through the activation of TFEB nuclear translocation in *M.tb* infected BMDMs and also in mice model [49].

### 2.14. Psychotropic Drugs

Psychotropic drugs are generally prescribed to patients with mental disorders [66] nonetheless; some psychotropic drugs from antidepressant and antipsychotic classes were evaluated for their ability to induce autophagy [35][50]. Nortriptyline, an antidepressant drug that functions by inhibiting norepinephrine and serotonin reuptake, was reported to induce autophagy in both HeLa cells and HMDMs against *M. bovis* BCG, *M.tb* strain H37Rv and two different clinical isolates. Nortriptyline modulates autophagy by increasing the rate of autophagosome formation [50]. Similarly, another antidepressant drug fluoxetine that inhibits the reuptake of serotonin was reported to enhance autophagy and increase the level of TNF-α in different cells viz., THP-1 cells, RAW264.7 cells and BMDMs against *M.tb* strain H37Rv [35]. Prochlorperazine edisylate, an antipsychotic drug that functions by inhibiting postsynaptic dopamine receptor, was observed to impair intracellular survival of mycobacteria by modulating autophagy in both HeLa cells and HMDMs. This drug reduces autophagic flux and increases the acidity of lysosomes which results in a concomitant reduction in intracellular mycobacteria [50].

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