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Mini-review

Identifying modulators of Synphilin-1 an AMPK modulator for potential therapeutic benefits

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Diabetes, Obesity, Non-alcoholic fatty acid liver and cancer, are some of the metabolic disorders of great concern worldwide. Although dietary habits and lifestyle play important roles in mitigating these health concerns. Nevertheless, the role of cellular regulators which act as molecular switches might provide us better understanding on the molecular trajectory of diseases alleviation. The human body is a complex system made up of diverse biomolecules that execute different biological processes or functions. While performing a biological function or process, biomolecules like proteins or enzymes may work closely with one another to either facilitate or put a brakes on each′s performance. For example, it has been shown that Synphilin-1, a metabolic regulator, interacts with AMPK the well-known master metabolic regulator, and that this interaction enhances the activation of AMPK. The identification of modulators (activators/ inhibitors) of AMPK has significantly shed light on their potent role in alleviation of metabolic diseases. What effect will the modulators of a metabolic regulator companion bring forth? An activated AMPK is a double-edged sword. Can we strike a new interest in identifying activators/inhibitors of the master regulator companion Synphilin-1? In this scoping review, we discuss on the structure, functions, and interplay between the two cellular regulators (AMPK and Synphilin-1), the role of plant metabolites/compounds as potent modulators and the approach available in identifying protein-metabolite interaction with an aim at providing contributory insights towards discovering modulators of protein Synphilin-1. The articles for compiling in this review were retrieved from databases like PubMed and Google Scholar. The 3D image of proteins was retrieved from databases Uniprot and RCSB PDB.

Keywords: Energy homeostasis, Enzymes, Medicinal plants

Introduction

Persistent hyperglycaemia is one of the most common characteristics of diabetes. It is a chronic metabolic disorder caused due to lack of insulin production or inadequate responsiveness to insulin secreted by the β-cells of the pancreas. The IDF (International Diabetes Federation) Diabetes Atlas 2022 Report, reported 537 million adults with diabetes, and an estimated number of people affected by it may reach 783 million by 2045[1]. Type III diabetes (TIIID) or Alzheimer's diseases (AD) or "diabetes of the brain" as often been referred to, have also reported to show impaired insulin signalling or insulin insensitivity as causative factor towards its progression. As with Type II diabetes, insulin related therapeutic strategies were reported beneficial in AD therapies by slowing down disease progression or even halting their future complications. Defective insulin signalling leads to hyperglycaemia. In hyperglycaemic conditions, blood growth factors, proteins, and peptide hormones are highly glycosylated, leading to the formation of advanced glycation end products (AGEs). AGEs interfere with proper cellular signalling of these molecules, thereby predisposing to various diseases, such as kidney failure, cardiovascular abnormalities, glaucoma and peripheral neuropathy. Increased generation and, consequently, a build-up of AGEs result in an elevated risk of microvascular and macrovascular complications[2], which, in turn, may lead to an increased risk of cardiovascular disorders. In the endothelium, AGEs cause reactive oxygen species production and have been reported to block nitric oxide activity[3]. These conditions ideally y emphasis on targeting glucose uptake into cells to keep blood glucose levels in check.

Although dietary habits and lifestyle, apart from medical interventions, play an impact factor in mitigating these health concerns, the role of cellular regulators, which function as molecular switches, cannot be undermined to help us better understand

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the molecular trajectory of disease alleviation. This review highlights the scope of redirecting focus in identifying potent activators and/or inhibitors of metabolic switches of energy homeostasis, understanding their mechanisms of action, and aiming to forge a path towards identifying the therapeutic benefits associated with them.

Regulators of energy balance

To keep up with the demand for energy, mitochondria produce more ATP. To do so, they grow, reproduce, and increase in mass through a process called mitochondrial biogenesis. However, an inadequate number of mitochondria leads to mitochondrial dysfunction. When such a condition occurs, the electron transport chain becomes less efficient. As a result, synthesis of ATP molecules also becomes strained or diminishes. A number of metabolic diseases, musculoskeletal diseases, cardiovascular diseases, neurodegenerative diseases and even chronic infections have been associated with mitochondrial dysfunction[4]. Therefore, examining mitochondrial integrity is central, as mitochondria are the mediators of cellular energetics. The maintenance for a proportionate flux of ATP in the cells is governed directly by some specialised and important homeostasis enzymes such as the 5' Adenosine Monophosphate-activated protein kinase (AMPK) and Synphilin-1. The enzyme AMPK plays vital function in mitochondrial biogenesis. It is therefore, at the same time important to keep in mind this significant aspect[5].

AMPK

The AMPK (E.C 2.7.11.31) is an approx 145 kDa serine/threonine protein kinase, which is highly conserved across all eukaryotic species. Expressed in cells of liver, muscles and kidney, it is a heterotrimeric enzyme complex composing of the α subunit with catalytic function a β subunit with a scaffolding function and the γ subunit with regulatory function (Fig. 1). The predominant function of AMPK is that it senses status/levels of energy in all eukaryotic cells besides many other functions (Fig. 2).

Structure

The AMPK α subunit has at the N terminal a catalytic[6] or kinase domain (α-KD). This α-KD domain in itself has two lobes or portions, a smaller N portion and a larger C portion, which are comprised of β sheets and α helices, respectively. In addition to these α helices, the C portion also contains the critical Thr 172 phosphorylation site. An adjacent autoinhibitory domain comprised of a group of three short α helices and hence the reference α-AID helix can be located in the AMPK α subunit[7]. Under low AMP levels, the α-AID helix inhibits the α-KD by binding to the α-KD. A linker peptide α-linker connects the α-AID helix to the C terminal domain of the α subunit (α-CTD). The α-linker also contains a regulatory motif (α-RIM) which serves as an interacting motif in the allosteric regulation of 5′-AMPK by nucleotides. Any mutations in the α-RIM or its interacting partner- γ subunit abolish such activation[8]. The α-CTD has an S/T loop (about

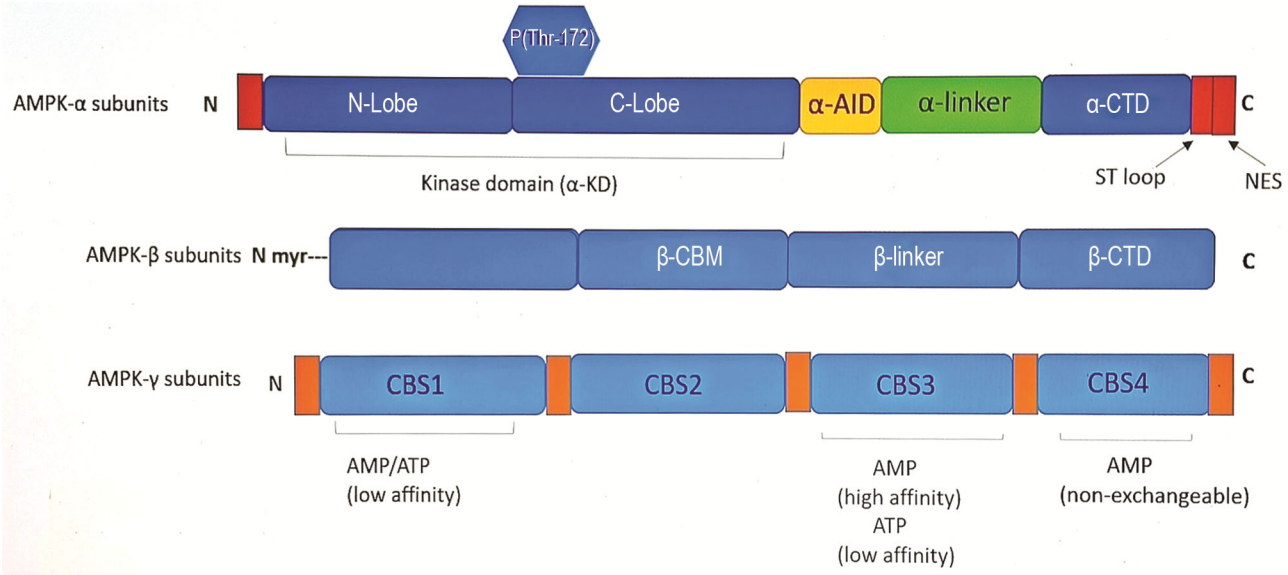

Fig. 1 — Structure of AMPK subunit.

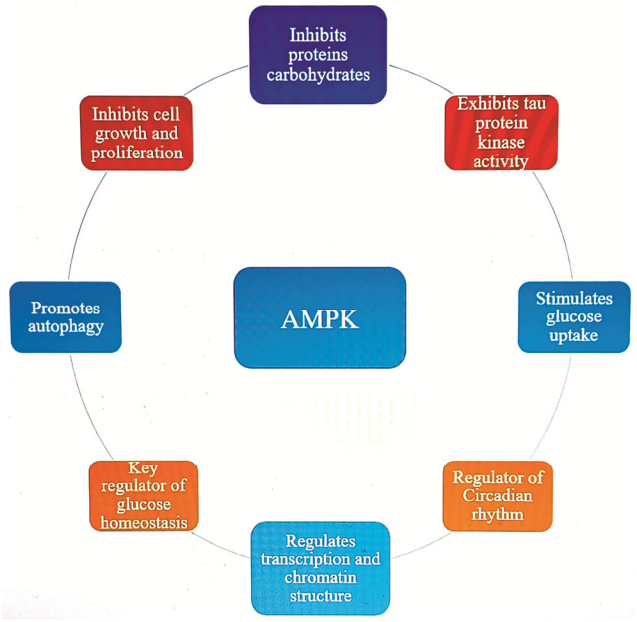

Fig. 2 — Physiological roles associated with AMPK.

50 residues) which contains within it an Akt phosphorylation site at Thr 496 in case of AMPK α1 isoforms[9]. In addition to Akt, other kinases may at the same or different sites regulate phosphorylation/ dephosphorylation of Thr 172, thereby permitting AMPK crosstalk with other signalling pathways[10,9]. A NES portion precedes the ST region of an α-CTD domain.

The β subunit consists of a carbohydrate binding module (β-CBM) as the core element of the subunit, a myristolyated N-terminal portion and a carboxy terminal end. The carboxy terminal is separated yet also linked to the carbohydrate module by a linker region. An activated AMPK can autophosphorylate at Thr148 residue within the β-CBM. The β-CBM has also been speculated to allow AMPK to sense and regulate glycogen synthesis. In addition, the β-CBM has yet another significant role of interacting with α-KD N portion called ADaM site and this interaction favours binding of endogenous metabolites and synthetic activators of AMPK and hence the name ADaM[10,9]. AMPK β subunit carboxy terminal forms an extended sheet with AMPK α and γ subunits[7].

The AMPK γ subunit comprising of a 60 residues sequence motif termed the cystathionine-beta-synthase (CBS) domain or the CBS repeat[10] that are repeated four times viz., CBS1-4. Two of the repeats assemble to form a domain referred to as the Bateman domain[7] and the resultant cleft formed from the combination serves as the binding site for adenosine containing ligands such as ATP, ADP and AMP[11]. CBS1, CBS 3 and CBS 4 are the adenosine nucleotide exchange sites. CBS 1 has a lower affinity for AMP while CBS3 has a much higher affinity for AMP. CBS4 exclusively binds AMP. It was speculated that the presence of an Arginine (Arg) instead of Aspartate (Asp) may be the probable reason for no AMP/ATP association with CBS2 domain. Additionally, adenine dinucleotides NADH and NADPH also interact with the γ sites[12]. AMPK γ subunit has additional allosteric binding sites identified as γ-pSite1 and γ-pSite for binding of activators like the 5 (5 hydroxyl-isoxazol-3-yl) furan-2-phosphonic acid C2 compounds. These sites are distinct from, however, overlaps with the nucleotides binding sites[13].

Altogether three allosteric binding sites have been reported with AMPK (a) - the γ sites, that binds adenosine nucleotides and C2 compounds, (b) the Carbohydrate binding module within β subunit, and (c) the ADaM (Allosteric Drug and Metabolite) site[10].

Regulation

Physiological processes such as hypoxia, glucose deprivation leads to alterations in cellular AMP: ATP ratios, rise in Ca^{2+} concentration and influences action of hormones, cytokines and adipokines. Such alterations stimulate AMPK, which then in its activated state acts upon its downstream targets by (i) switching on/off enzyme′s catalytic activity or (ii) triggering protein-protein interaction thereby altering protein subcellular localisation or targeting it for degradation.

The three mechanisms of AMPK activation involve (a) Canonical regulation, activation and subsequent phosphorylation responsive to AMP: ATP or ADP: ATP ratio consequently preventing its dephosphorylation in conjunction with stabilising the already phosphorylated state of enzyme[11,14,15]. (b) by Ca^{2+} mediated pathway or the Calcium-Calmodulin-dependent protein kinase kinase β (CaMKK) pathway[16] where CaMKKβ associates with AMPK through their kinase domains[17] an activation triggered by a rise in cytosolic Ca^{2+} and in response to hormones and extracellular agonists, and is independent of AMP[18] and via (c) non-canonical pathway or the glucose sensing mediated pathway, since here the enzyme aldolase act as the sensor of glucose availability. Non-canonical pathway acts in an AMP: ATP independent mechanism.

By sensing any increase in mono/di to tri phosphate nucleotide ratios, AMPK can respond to energy stress, restoring energy balance by inhibiting or downregulating energy-consuming anabolic processes while favouring the upregulation of energy-generating catabolic processes. AMPK plays vital roles in regulating glucose transport into cells[19] by regulating glucose transporter trafficking[20,21]. Activated AMPK also keep a check on fatty acid synthesis by inhibitory phosphorylation of enzymes such as acetyl-CoA carboxylase synthase thereby regulating those metabolic pathways linked to diabetes. Furthermore, Ramamurthy *et al.*[22] showed that during neuronal development, activated neuronal AMPK inhibits axon outgrowth and dendritic arborisation, for adapting to metabolic stress suggesting the probable role of AMPK in mediating structural synaptic changes in brain cells and hence AMPKs role in brain energy administration. AMPK activation can be both neuroprotective and proapoptotic depending of cell types, intensity and duration of activation and nature of insults this however, is also influenced by what enzyme subunit isoforms are involved. As pointed out by Kong *et al.*[23] conditional deletion of AMPK1 enhances a number of regenerative signalling pathways suggesting inhibition of AMPK may offer therapeutic strategy to enhance regeneration following a spinal cord injury. Because AMPK possesses the capacity to remodel metabolism, it is an extensively pursued target for the alleviation of several metabolic disorders.

To reiterate, energy balance is essentially desirable for proper maintenance of the body system. The brain is the organ that demands a comparatively high amount of energy the rest of the body's organs. Neurons, in particular, are dependent on mitochondria for ATP production[24]. There are several genes and proteins that work in conjunction to regulate the physiological function in the body. In addition to the well-regarded master regulator AMPK, which maintains energy homeostasis by regulating AMP/ATP, we focus on another energy homeostasis regulator, Synphilin-1, a protein that has been frequently linked to neuro-metabolic processes but is less studied.

Synphilin-1

Synphilin-1 is a cytosolic protein that is expressed in the brain and other tissues viz., heart and placenta. It is a 919-amino acid protein. In humans, the Synphilin-1 protein is encoded by the SNCAIP25 gene.

Structure

Synphilin-1structure is curated as a probable homodimer or heterodimer of isoform 1 and isoform 2[25,26]. Synphilin-1 contains 6 ankyrin-like repeats. Ankyrin repeats are protein motifs that permit protein-protein interaction. Synphilin-1 also contains a coiled-coil domain and harbours five ATP-binding motifs (Fig. 3) suggesting that Synphilin-1 may regulate cellular energy levels[27]. Molecular functions of Synphilin-1 include ubiquitin protein ligase (Parkin, a PD linked gene product) binding via a non-classical, proteosomal-independent manner involving Lysine 63 (K63) polyubiquitin chain formation, and this event may be involved in formation of Lewy body inclusions associated with Parkinson′s diseases (PD)[28,29]. The protein is also involved in regulation of neurotransmitter secretion, dopamine metabolic process, amyloid fibril formation, regulation of inclusion body assembly, cell death and mechanotransduction[26,30,31] (Fig. 4).

Synphilin-1 is an energy homeostasis regulator that functions by raising intracellular ATP levels[27]. Synphilin-1 transgene expression has shown to induced hyperphagia. Studies by Li *et al*[32] reported impaired glucose tolerance and an increased triglycerides and fat deposition in human Synphilin-1 transgenic mice as a result of hyperphagia induced obesity and Liu *et al.* [33] reported that overexpression of human Synphilin-1 in nerve cells of *Drosophila* is also associated with increase in food consumption and hence body mass. In context of neurodegenerative diseases, Synphilin-1 plays significant role in cytoplasmic inclusions, formation and neurodegeneration via its interaction with alpha-

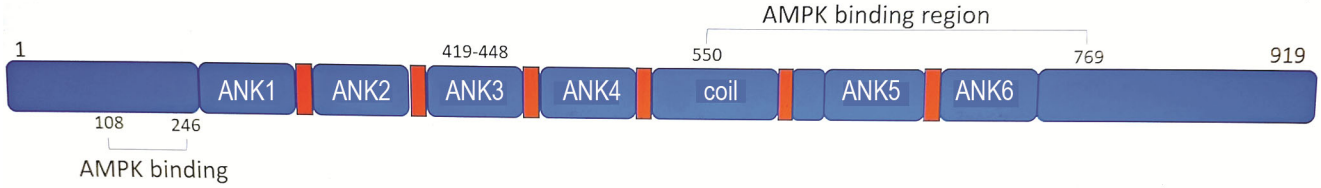

Fig. 3 — Structure of Synphilin-1.

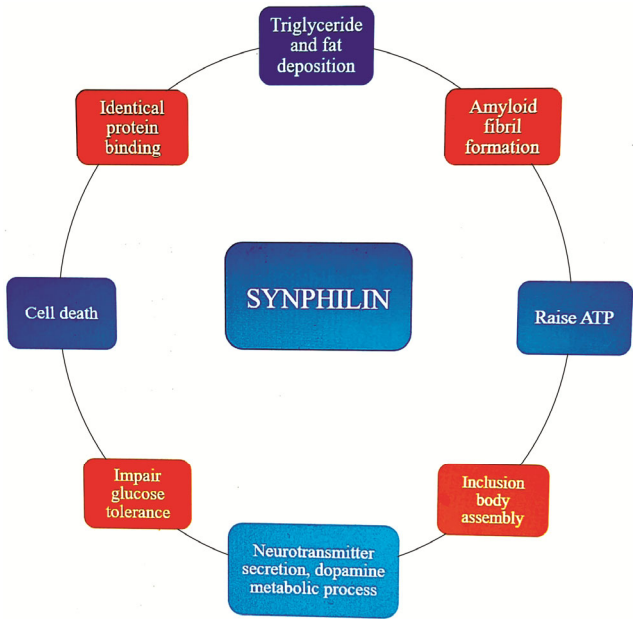

Fig. 4 — Pysiological roles of Synphilin-1.

synuclein in neuronal tissue. Whereas, Shishido *et al.*[34] suggested that synphilin-1 is involved in saving mitochondrial function thereby protecting against dopaminergic cell death. Their results further indicated that Synphilin-1inhibits ROS production and apoptosis and may play neuroprotective roles in the pathogenesis of Parkinson′s diseases (PD). Mutation R621C in Synphilin-1 protein is associated with pathogenesis of Parkinson′s disease[35-37].

Interaction between regulators of energy balance AMPK and Synphilin-1

AMPK is regarded as the central metabolic regulator of energy homeostasis. To achieve this regulation, AMPK functions by inhibiting processes that consume ATP while facilitating ATP-generating processes. Liu *et al*. elucidated the role of Synphilin-1 as a controller of energy homeostasis, depicting the protein function mainly by raising intracellular ATP levels speculated due to the presence of ATP binding motifs[27]. Recent findings provided evidence of the interaction between the two regulators[38]. Co-immunoprecipitation and pull-down assays revealed that AMPK binds Synphilin-1 at two sites: one within the 108–246 aa region and another within the 550–769 aa region. Furthermore, it was revealed that knockdown of Synphilin-1 by siRNA downregulates AMPK phosphorylation whereas compound C (AMPK inhibitor) reduced interaction between AMPK and Synphilin-1[38]. Additionally, Liu *et al.*[33] conducted *in vivo* studies using *Drosophila* flies transgenically expressing human Synphilin-1 which confirmed a significant increase in Thr172 phosphorylation by 3.4 fold. Co-expression of transgenic synphilin-1 with AMPKα siRNA showed a remarkable decrease in total AMPK and phosphorylated AMPK. Synphilin-1 is also a binding partner of α-synuclein. The α-synuclein co-localises with PIN1 stores up in the lewy bodies and lewy neurites in parkinsons diseases[39]. PIN 1 is an isomerase precisely a prolyl cis/trans isomerase (PPIase). PIN 1 has two domains: domain PPIase at its carboxy terminus and a second domain with conserved tryptophan residues WW domain at the amino terminus. WW domain has protein interaction activity selectively towards proteins bearing S/T-P motifs and this binding or interaction is phosphorylation dependent. The PPIase domain on the other end possess catalytic activity i.e., isomerization activity. PIN 1 binds Synphilin-1 via its Ser-Pro motifs at positions 211 and 215. PIN 1 has also been shown to interact with AMPK and that the interaction downregulates AMPK activity[40]. AMPK binding site of PIN-1 is located in its amino terminal WW domain and encompasses amino acids 1–44. PIN 1 can bind with AMPK and suppress its phosphorylation by inducing PP2A activity. A mutation from Ser to Ala at Ser176 site in AMPK kinase domain will result in a consequential loss of binding between AMPK and PIN1 indicating a crucial interaction of AMPK with PIN-1 at Ser176 residue. As Li *et al.* deliberated, the interaction between Synphilin-1, AMPK and PIN 1 provided pivotal notion in understanding the role of AMPK interacting partner. This thus identifies an interest in detecting potential modulators of such a protein with therapeutic prospects.

Significance of activators and inhibitors of AMPK in treating metabolic diseases. Can these too be potential Synphilin-1 modulators?

The diverse functional attribute of AMPK makes it an appropriate target in modulating the progression or alleviation of metabolic disorders such as diabetes type II, non-alcoholic fatty liver disease and cancer. Activators of AMPK may be broadly categorised in two classes (a) those stimulating AMPK in response to adenosine nucleotide concentrations and may, therefore, be called *Indirect activators;* and (b) those that activate AMPK by inducing a conformational change without any significant changes in

AMP/ADP/ATP ratios as, the *Direct activators. Indirect activator* compounds include (a) inhibitors of mitochondrial respiratory complex I (e.g., synthetic compounds (Thiazolidinediones, Biguanides) and natural compounds (Berberine, Resveratrol), (b) ATPase inhibitors (e.g. Polyphenols) (c) α lipoic acid via increasing Ca^{2+} concentration, while, *Direct activators* include synthetic activators like (a) AICAR an AMP mimetic, (b) Thienopyridone (A-769662) an allosteric activator and (c) Salicylate a natural plant compound.

Natural products the potent modulators

As with diabetes and other metabolic diseases, natural products have been known to exert neuroprotective effect as well. Medicinal plants have been reported to slow down the advancement and symptoms of AD and PD[41]. Extracts as well as compounds (metabolite) from medicinal plants have been intensively examined for their effects on AD[42]. These active compounds obtained from plants such as, *Caralluma diffusa* W*, Cryptolepis sanguinolenta, Radix Stephania tetrandra, Panax ginseng, Coptidis rhizome, Berberis vulgaris, Carthamus tinctorius, Crocus sativus, Berberis bealei Fortune, Coptis chinensis Franch and Phellodendron chinensis, Huperzia serrata* have been reported to exhibit various beneficial neuroprotective functions via a number of mechanisms. This includes antioxidant activities[43,44], anti-neuroinflammatory activities[45,46], anti-amyloidogenic activities[47,48], anti-tau aggregation activities[49,50] and anticholinesterase activities[51,52] respectively.

Similarly, natural products exert their effect against PD[53,54] through various pathways leading to increased dopamine level (Safflower[55], *Delphinium denudatum*[56]) and mitochondrial complex I activity (*Tinospora cordifolia*[57])*,* reduced dopaminergic neuronal loss, microgliosis (*Panax ginseng*[58]), acetylcholine levels (Safflower[55,59]) and decreased malondialdehyde (MDA) levels (*Tinospora cordifolia*[57], *Hypericum perforatum*[60], *Hibiscus asper leaves*[61], *Delphinium denudatum*[56]*, Bacopa monniera* Linn[62], *Althaea officinalis* L.[63]). In addition, flavones from extracts of *Chrysanthemum morifolium*[64,65]*, Carthamus tinctorius* L.[59] and *Panax ginseng*[58] have been reported in the suppression of α-synuclein aggregation, the very same property exhibited by Synphilin. Flavones from *Robinia pseudoacacia*[66] while extracts of *Turnera diffusa*[67] showed reduced proinflammatory cytokines expression as well as neuroinflammatory actions. Moreover, extracts of *Rhus verniciflua*[68] offered neuroprotective property via inhibition of ROS-Ca^{2+}- Bax/Bcl-2-caspase-3 and ROS-Ca^{2+}- p38 pathways thereby suppressing apoptosis against 6-hydroxydopamine (6-OHDA), a neurotoxin employed in PD generation for *in vitro* studies.

A comparative observation on the role of plant compounds in both of these metabolic regulators-AMPK and Synphilin-1 can be drawn. Metformin is an example of a (biguanide) plant derived compound with anti-hyperglycaemic activity, which through its inhibition of mitochondrial complex I raises AMP: ATP ratio, thereby, indirectly activates AMPK[69,70]. Salicylate, a hormone produced by the willow bark and many other plants, in response to pathogen stress on the other hand, directly binds and activate AMPK by binding to its ADAM site[71]. Findings made by Betarbet *et al*[72], Sherer *et al*[73], showed that chronic treatment of rotenone, a mitochondrial complex I inhibitor, in rats exhibited features of Parkinson′s disease. Rotenone treatment is associated with induced oxidative stress, modest ATP depletion and cell death. Overexpression of synphilin-1 showed protection against rotenone-induced cell death by downregulating caspase-3 activation and downstream PARP cleavage[74]. However, in another account, treatment with antioxidants Coenzyme Q10 and α-tocopherol diminished toxicity caused by the mitochondrial inhibitor[73]. α-tocopherol, or Vitamin E, is an antioxidant abundantly present in plants[75]. Its anti-proliferative and free radical scavenging activity marks its therapeutic value in treatment of metabolic diseases such as cancer, diabetes and obesity where oxidative stress plays vital role. Hence, in addition to their antioxidant properties, plant metabolites may act via pathway inhibition/activation or via direct interaction; other mechanisms of action are yet to be determined. Extensive research may provide an engrossing ground for establishing the role of and for validating any beneficial effect of Synphilin-1 activators from natural products.

Methods and tools for studying protein-metabolite interactions

In an effort to probe for and identify plant compounds or metabolites, understanding and deciphering the intricate interactions between metabolites and proteins is a challenging yet

important aspect. Protein-metabolite interaction methods have been broadly categorised under the following heads; (a) protein affinity for a metabolite (AP); (b) protein-metabolite complexes (PMC) stability dynamics towards a chemical reaction (oxidation (SPROX), thermal influence(CETSA/TPP, PISA), solvent (SIP), or presence of biological inhibitors within the system(LiP-MS); (c) chemical modifications of metabolite functional groups for enhanced protein binding (Chemoproteomic profiling); (d) protein structures elucidation (NMR, MIDAS), immobilization (DRaCALA) and purification techniques of either labelled or unlabelled PMC (TAP, PROMIS) and (e) other biophysical methods(SPR, ITC, Cryogenic electron microscope, Microscale thermophoresis)[76].

In addition, a number of *in silico* databases are available for acquiring valuable information on protein-metabolite interactions, these include Protein Data Bank (PDB), BRaunschweig ENzyme DAtabase (BRENDA), ChEMBL, DrugBank, Binding DB, Therapeutic Target Database (TTD), and PMI-DB[76].

Discussion

AMPK functions as a double-edged sword. As a regulator of glucose homeostasis, its activation however, imparts undesirable effect in cells suffering from hypoxia and glucose deprived cells such as tumorigenic cells and tissues. A well-regulated physiologic effect of the enzyme in such cells and tissues hence is an absolute necessity. Another point of consideration is that, although these interacting partners may seem to need one another, they appear to exert contrasting metabolic effects. Transgenic mice expressing Synphilin-1 reported increased triglycerides and fat deposition[32], an activated AMPK inhibits fatty acid synthesis[77]. Whereas AMPK activation facilitates glucose uptake[19], impaired glucose tolerance was reported in Synphilin-1 transgenic mammals[32] because of Synphilin-1 induced hyperphagia. These phenomena although may seem indistinct but may be affiliated to the resultant binding interaction between Synphilin-1 and PIN 1 with AMPK and may be yet other unknown binding partners of AMPK. As much emphasis on Synphilin-1 modulators has not yet been placed distinguishing and evaluating their effect on the protein therefore, might offer therapeutic benefits. Additionally, any significant outcome may, in turn, confer interacting partners such as Synphilin-1 as beneficial co-targets or alternative molecular targets for alleviating metabolic diseases (Fig. 5).

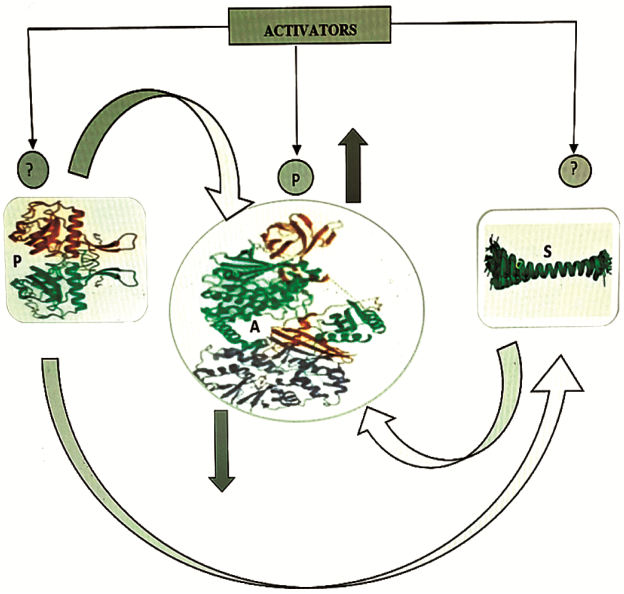

Fig. 5 — Illustrates the interaction between AMPK with Synphilin-1 and PIN-1. Interaction of PIN-1 (P) with AMPK (A) results in downregulation of AMPK activation which is indicated by the darker arrow pointing downwards whereas Synphilin-1 (S) interacts with AMPK (A) resulting in the upregulation of AMPK activation also indicated by the darker arrow pointing upwards. PIN-1 also interacts with Synphilin-1 as indicated in the figure. What role will activators of these proteins play in this signalling cascade? 3D structures of PIN-1, AMPK and Synphilin-1 proteins retrieved from RCSB PDB and Uniprot database.

Conclusion

The role of naturally occurring compounds that exert their activating effect via different mechanisms on AMPK has been discussed. Natural activators of AMPK have a significant impact on alleviating insulin resistance, type II diabetes, and secondary micro- and macrovascular complications of diabetes, as well as on wound healing associated with diabetes. Their significance has become more important with the incidence of COVID-19 wherein diabetes poses as a serious risk factor. Recent insight on Synphilin-1 binding AMPK at two regions, one being an ANK-repeat region (housing a predicted protein–protein interaction domain) designated as the 108–246 aa region and another at 550–769 aa offers the possibilities to delve and further understand the synphilin-1 - AMPK signalling pathway which may consequently enhance our understanding on their participatory role in regulating metabolic syndrome as a whole. A comprehensive understanding of the

Synphilin-1 protein structure itself is of a prime importance. One fascinating point to consider is the role that similar known activators/inhibitors of AMPK or novel activators/inhibitors might play compared to Synphilin-1. An elucidated study on activators/inhibitors, with emphasis on medicinal plant compounds that are safer drug candidates, may further enrich and provide insights into their role/effect on the AMPK-binding Synphilin-1 protein. Therefore, shifting focus to the floral community may be beneficial, as natural products of medicinal value are gaining momentum.

Conflict of interest

The authors have no conflict of interest to declare.

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