Unveiling novel longevity-regulating mechanisms of phytogenic adaptogen Phytocee TM through a computational biology approach

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Research Article

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Abstract

Phytogenics is a promising and novel sector in animal health. Indian botanicals have been shown to protect animals from various diseases and health stressors, which include nutritional, environmental, biological, and chemical stressors. These stressors may cause sudden mortality in the animals and are a matter of concern among farmers, which Phytocee^{TM} can address. It consists of scientifically validated (LC-MS/MS) phytochemicals belonging to the classes of triterpenoids, hydrolysable tannins, and withanolides that help enhance the adaptogenic potential of the animals. The adaptogenic potential of an animal is associated with prolonging their lifespan. This research investigated the pathway-focused approaches for increasing longevity in animals at a cellular level by observing their differentially expressed genes (DEGs): *FOXO, AMPK, SIRT1, and mTOR* using computational tools for gene enrichment: DIGEP Pred2.0, which showed significant modulation of the DEGs (1.25e-159), especially for the enriched term “longevity regulating pathway”. Pathway mapping using SHINYGO0.82, KEGG, showed significant mapping of these genes in the enriched pathway. Network pharmacology was done to detect protein-protein interactions for these DEGs using INPUT2.0. The heat maps and flowerpot Venn diagrams were generated for enriched pathways using SR-PLOT, which showed that the maximum genes were responsible for regulating the longevity of the animals. The study concluded with a possible molecular pharmacology of Phytocee^{TM,} suggesting that the product may have helped overcome stressors by increasing the lifespan of various animal species, including poultry, swine, and aquatic animals. The possibility can be further validated through the wet lab trials.

Introduction

The global health market sees great potential in the adaptogen market. In the supplement industry, a shift toward sustainable animal production is increasing demand for herbal products over chemical ones. Many botanicals such as *Emblica officinalis* (Amla), *Ocimum sanctum* (Tulsi) and *Withania sominifera* (Ashwagandha), *Bacopa monneiri* (Brahmi), *Tinospora cordifolia* (Guduchi) and *Glycyrrhiza glabra* (Licorice) have been shown to have excellent resistance to different kinds of stressors and improve animal health. These adaptogenic plant-based products and their phytochemicals have been a popular and effective choice in animal food and feed supplements. [1–4]

Adaptogens play a vital role in animal health by reducing multiple stresses during their life cycle. The various types of stressors in animals can be attributed to nutritional deficiencies or compromised management systems on farms, which may include inadequate ventilation, an ammoniacal smell in the environment, or internal stressors such as a lack of immunity to infectious diseases and susceptibility to thermogenic stress. Due to all these stressors, there is a heavy risk of high incidences of mortality, that are a cause of great concern in industry. Enhancing the adaptogenic potential of the animals is the pressing need to alleviate stress levels, thereby reducing sudden mortality. Adaptogenic potential is an umbrella term for resilience to stress, immunity and productivity of the animals These biological components show an augmented effect to prolong the lifespan of an animal. There is a need to study the mode of action of the phytogenics for their adaptogenic potential.

Phytocee™, is a synergistic combination of these globally known adaptogens. It has been shown to have a significant impact on thermogenic stress markers. Pharmacological validations to study the mechanism of action of Phytocee™ (200g/ton feed) has shown an influence on thermogenic stress. [5–6] As scientific research progresses, the in-silico tools reveal the possibility of deducing and identifying evidence-based mechanisms of actions involving bioenergetics, anti-inflammatory, and antioxidative mechanisms that were decoded. These mechanisms were strongly associated with enhancing the adaptogenic potential, contributing to the prolonged lifespan of the animals. For this purpose, various *in-silico* models were used to predict the possible pharmacological mechanism of action of the phytochemicals in increasing the longevity of the animals.

The signaling regulates longevity mechanisms; the binding interactions of insulin and its receptor activate the P13K-Akt signaling pathway to produce AC-mediated cAMP, acting on the CREB and further activating the FOXO signaling to employ cellular free radical scavengers SOD2 and CAT that are involved in cell detoxification, the mTOR signaling pathway for inhibition of redundant protein synthesis. The literature has highlighted the importance of insulin signaling, mTOR, and other proteins and pathways in regulating a cell's longevity. [7] Studies in *C. elegans* have shown that autophagy genes are essential for the lifespan extension observed in mutants with reduced IIS, mTOR signaling, or dietary restriction. This suggests that autophagy acts downstream of these pathways to mediate their effects on longevity. [8] Endurance plays a significant role in regulating longevity at the cellular level by signaling through the AMPK pathway, which is activated upon sensing low cellular energy levels and acting on sirtuin to promote mitochondrial biogenesis and maintain cellular bioenergetics. Literature studies have reported that the overexpression of SIRT6 enhances DNA repair mechanisms and maintains telomere integrity, contributing to improved cellular function during aging [9].

Thus, the present study illustrates the role of phytogenics through the validated presence of unique phytochemicals, as determined by LC-MS/MS, and unveils their role in adaptogenic activity via longevity mechanisms, as elucidated through *in-silico* studies.

Materials and Methods

LC–MS Conditions

The molecular ion profiles and fragmentation patterns of the selected phytoconstituents were investigated using a Sciex QTRAP 4500 triple-quadrupole Mass spectrometer, coupled with a Shimadzu LC-40D XR, in both positive and negative electrospray ionization modes, within the scan range of m/z 50–550, using Analyst software to record the data.

Target identification and retrieval of protein sequences

The target proteins were identified through a systematic literature review and by searching curated pathway databases implicated in pathways relevant to linking stress, insulin resistance, mitochondrial

biogenesis, and protein processing accuracy, which regulate cellular longevity. The target genes, along with their annotations, were retrieved in FASTA format through UniProtKB https://www.uniprot.org/. *Forkhead box O (FOXO1, FOXO3), peroxisome proliferator-activated gamma receptor coactivator alpha (PPARGCA), sirtuin 1 (SIRT1), mechanistic target of rapamycin (mTOR), adenosine monophosphate kinase (AMPK)*, and other pathways relevant to enhancing cell longevity were subjected to ShinyGO0.82 https://bioinformatics.sdstate.edu/go/.

Gene enrichment & KEGG pathway

The ligand files retrieved from https://pubchem.ncbi.nlm.nih.gov/ were uploaded to the DIGEP Pred2.0 https://www.way2drug.com/digep-pred/ for the regulation of unique target genes. The entire protocol was followed at the activator Pa > 0.5. The modulated gene set was mapped on an enrichment bubble in INPUT2.0 https://cbcb.cdutcm.edu.cn/INPUT/Home/ based on the gene count and p values. Gene network analysis was done for the data generated. The genes linking to the longevity regulation pathways were analyzed for the following parameters: gene count, P-value, signal and strength. Gene count indicates the number of relevant genes that were modulated. P-value indicates the significance of modulated genes in the gene set. Some genes may have high significance, but they may be less in count, and some genes may be high in count and have low p values or of less significance. Signal gives a balance between the two metrics. Strength parameter indicates a higher count of genes with more significance. The modulated gene set created by the DIGEP Pred2.0 tool https://www.way2drug.com/digep-pred/ was mapped on the KEGG genome database to view the longevity-regulating pathway analysis (KEGG ID: hsa04211). The annotation of the signaling pathway was extracted from the (NCBI). The reactome pathways diagrams for the differentially expressed genes were produced to elucidate the cellular signaling pathways using https://reactome.org/.

Venn diagram and Heatmap analysis

A Venn diagram was drawn based on the modulated gene set. The modulated gene sets were mapped on a matrix heatmap in the SR-PLOT https://www.bioinformatics.com.cn/en based on: Phytochemicals present in the Phytocee as gallic acid (1), ellagic acid (2), ursolic acid (3), withaferin A (4).

Results and Discussion

Monogastric animals reared globally are exposed to various internal and environmental stressors; therefore, enhancing their resistance to stress is a pressing need for the continued exponential growth of the economy. Stress is inversely proportional to the lifespan of the animals. Therefore, reducing stress and enhancing cell longevity is of utmost importance. This can be achieved by strengthening the adaptogenic potential of the animals, which enables them to overcome the significant stress imposed by environmental conditions. This product consisted of adaptogenic classes of hydrolysable tannins, triterpenoids, and withanolides whose structures were analyzed for chemical composition in LC-MS/MS.

The phytochemicals from Phytocee™ were confirmed by LC-MS/MS from different classes with structures indicated in Fig. 1. Triterpenoids, namely ursolic acid, exhibited a protonated molecular ion at m/z 457 [M + H] +. The MS/MS fragmentation produced a major ion at m/z 439 [M + H − H2O] +, indicating a neutral loss of water. Further fragmentation yielded ions at m/z 411 [M + H − COOH] + and m/z 393, confirming the triterpenoid skeleton of ursolic acid. The withanolides, such as withaferin A, exhibited a protonated molecular ion at m/z 471 [M + H] +, which upon fragmentation yielded a major ion at m/z 453 [M + H − H2O] +, indicating the elimination of water. Additional ions at m/z 435 [M + H − 2H2O] + and m/z 417 confirmed successive water losses, characteristic of withanolide lactone fragmentation. The hydrolysable ion gallic acid was detected in the negative ion mode with a molecular ion at m/z 169 [M − H] −. The MS/MS spectrum exhibited fragment ions at m/z 125 [M − H− CO2] −, corresponding to the decarboxylation of gallic acid, and m/z 97 [M − H − COOH − CO] −, confirming its polyphenolic structure. The hydrolyzable tannins, namely ellagic acid, showed a deprotonated molecular ion at m/z 301 [M − H] −, with characteristic fragmentation ions at m/z 257 [M-H-CO2] − and m/z 229 [M-H − COOH − CO] −, corresponding to sequential decarboxylation and carbonyl losses. The other tannins were confirmed in negative ionization mode as gallic acid (m/z 169) fragmented to yield m/z 125 and 97, indicating decarboxylation and further loss of CO groups, while ellagic acid (m/z 301) produced fragment ions at m/z 257 and 229, corresponding to successive CO_2 and COOH eliminations. Collectively, these fragmentation patterns agree with literature reports, thereby confirming the structural identity and authenticity of the compounds analyzed, which can be further taken up for in-silico studies. The analytical results of the compounds are shown in Supplementary Figure S1.

The gene datasets that were collected from DIGEP Pred 2.0 (https://www.way2drug.com/digep-pred/) and the results were recorded in Table 1. The parameters: gene counts, p-values, signal, and strength for all the active constituents were recorded in Table 2.

Table 1
Modulated gene list for longevity regulating pathway (KEGG ID: hsa04211).

KEGG Pathways	Phytocee	Modulated gene list
	Withaferin A	ADCY3, ADCY5, AKT2, AKT3, ATF2, ATF4, BAX, CREB3L2, FOXO1, FOXO3, IRS2, NFKB1, NRAS, PIK3CA, PIK3R1, PPARG, PRKAB1, PRKAG2, SESN2, SESN3, SIRT1, SOD2, TP53, TSC1, ULK1
	Gallic acid	ADCY3, ADCY5, AKT2, AKT3, ATF4, ATG101, ATG5, BAX, CREB3, CREB3L1, CREB3L2, EIF4E, FOXO1, FOXO3, IGF1R, IRS2, KL, KRAS, NFKB1, NRAS, PIK3CA, PRKAB1, PRKAG2, RELA, SIRT1, TP53, TSC1, ULK1
Longevity regulating Pathway	Ursolic acid	ADCY3, ADCY5, AKT2, AKT3, ATF4, ATG101, ATG5, BAX, CREB3, CREB3L1, CREB3L2, EIF4E, FOXO1, FOXO3, IGF1R, IRS2, KL, KRAS, NFKB1, NRAS, PIK3CA, PRKAB1, PRKAG2, RELA, SIRT1, TP53, TSC1, ULK1
	Ellagic acid	ADCY3, ADCY4, ADCY5, ADCY7, ADCY9, ADIPOQ, ADIPOR1, AKT1, AKT1S1, AKT2, ATF2, ATF4, ATG101, ATG5, BAX, CAT, CREB1, CREB3, CREB3L1, CREB3L2, CREB5, EIF4E, EIF4EBP1, FOXO3, HRAS, IGF1, IGF1R, INS, IRS1, IRS2, KL, KRAS, MTOR, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PPARG, PPARGC1A, PRKAB1, PRKACA, PRKAG2, RB1CC1, RELA RPTOR, SESN1, SESN2, SIRT1, SOD2, TP53, TSC1, TSC2, ULK1, ADCY1, ADCY2, ADCY3, ADCY6, ADIPOR2, AKT3, APPL1, ATF6B, CAMK4, CAMKK2, CREB3L3, EHMT1, IRS4, NRAS, PRKAA2 PRKAB2, PRKACB, PRKAG1, RPS6KB1, SESN3

Table 2
Modulated genes with different parameters to measure their significance

Longevity regulating pathway			
Phytocee® Compounds	False discovery rate	No. of modulated genes	Signal
Ellagic acid *	1.27e-159	74 out of 87	30.94
Gallic acid *	3.27e-130	60 out of 87	26.88
Withaferin A	5.1e-50	25 of 87	15.94
Ursolic acid	1.24e-58	27 of 87	16.18

* The values denote highly significant modulation of genes regulating the longevity pathways (p < 0.01)

All the Phytocee™ compounds significantly modulated a total of 87 genes. Out of all the compounds, withaferin A showed the highest degree of modulation (FDR: 1.27e-159). It significantly modulated 74 genes, including genes responsible for stress and insulin resistance signaling, such as FOXO1, FOXO3, SIRT1, *and CREB3L2*. In the order of decreasing degree of modulation, gallic acid showed significant modulation (FDR: 3.27 e-130). A total of 60 genes involved in cellular energy homeostasis, stress, and

insulin resistance signaling pathways, such as FOXO1, FOXO3, IGF1, and PPARGC1A, were modulated with great significance by gallic acid. Highly significant modulation was shown by both ellagic acid and ursolic acid on the longevity-regulating genes. The genes that were modulated significantly for the pathways that help in promoting cellular fitness and longevity. The significant cellular pathways studied for the differentially expressed genes are demonstrated in Fig. 2.

High levels of significance were observed for *MAPK, GPCR*, and mTOR signaling pathways, suggesting energy biogenesis, protein synthesis, and modification of a living cell. The biological process of oxidative scavenging with the help of macroautophagy was also modulated by the compounds with great significance. A wide range of research articles have been published on the anti-stress, adaptogenic and pro-longevity properties of these phytochemicals. Withaferin A has been shown to activate AMP-activated protein kinase (AMPK) in myocardial tissue of mice thereby having an action on infarcts in mice [10]. Many clinical and animal trials have proved the efficacy of Withaferin A alone to show a significant reduction in stress levels which is attributed to downregulation of HPA axis activity and the root extracts showing lowered cortisol production and epinephrine levels post stress inducing exercises which added to a support to adaptogenic properties of a compound [11–13]. Researchers have proved that ellagic acid has the potential to regulate AMPK/P13k/mTOR pathways, thereby significantly reducing the angiogenic signaling [14]. Some experimental gene expression studies showed that supplementation of ellagic acid displayed upregulated expressions of CAT, dFOXO, ATG1, and SOD2 in ellagic acid-treated male flies, and upregulated expressions of dFOXO, CAT, and SOD2 in ellagic acid-treated female flies, which indicated the pro-longevity effects of the ellagic acid [15]. In the present study, the biological significance was also observed in the reactome pathways. In a few studies, Ursolic acid alone has been able to show adipogenesis-inhibiting effects by activation of the AMPK pathway. It plays a significant role in muscle protein anabolism through the mTOR pathway [16–17]. The direct impact of gallic acid alone was observed in the findings of Zhang et.al. (2023) on lipid metabolism via the AMPK-ACC-PPARα axis [18]. Gallic acid has also been found to show active inhibition of the PI3K-Akt signaling pathway [19].

The synergistic action of the compounds present in Phytocee ™ was reported by constructing the flower plot Venn diagram and heat maps to study the significance of the differentially expressed genes linking to the cellular longevity. Figure 3. Highly significant modulation (34 genes) was shown by the synergistic action of gallic acid and ellagic acid. It also represented all the common modulated genes (17 genes) by the product Phytocee™. The matrix heatmap showed that the phytochemicals indicated excellent modulation in the pathways determining the resistance and endurance of a cell exposed to significant amounts of stress. This synergy has been proven by Gallic acid and Withaferin A to modulate the AMPK pathway, improving energy efficiency and autophagy [20]. It enhances endurance, improves immune response, regulates stress hormones, and increases the longevity of cells, thereby reducing mortality in animals and contributing significantly to market potential.

Conclusion

The current elucidative mechanistic approaches have played a major role in deciphering the longevity regulating pathways. This may be a strong indicator of reducing mortality amongst the animals associated with significant economic concerns. The present *in-silico* data has helped to draw predictive conclusions on the synergistic activity of the Phytocee™ polyherbal combination upon the energy sensing, stress responses, insulin signaling, and post-translational modifications. This research has broadened our horizon in the areas of adaptogenic activity of natural phytochemicals and their role in regulating the longevity of a cell at molecular level. This study provides an excellent framework for developing a mechanism of action using cutting-edge technology, laying the groundwork for future studies.

Declarations

Author Contribution

Shamana K and Edwin R contributed in curation and the analysis of the original database. Jaishree SP has supported in generating the analytical data and phytochemical figures. Prashanth D and Aboli G contributed in the supervision of the data. Deepak M contributed in reviewing of the draft manuscript and supplementary files and providing resources required to publish this data.

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Figures

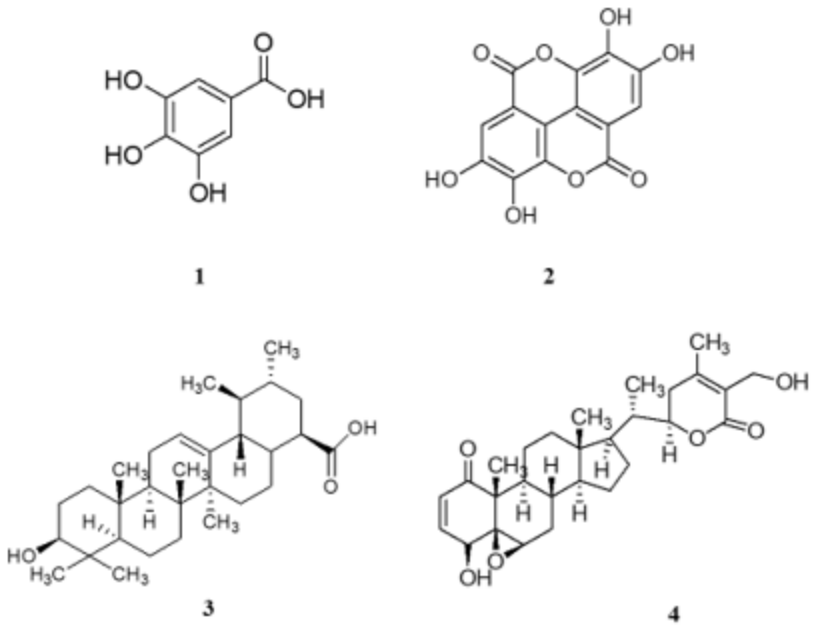

Figure 1

Phytochemicals present in the Phytocee as gallic acid (1), ellagic acid (2), ursolic acid (3), withaferin A (4)

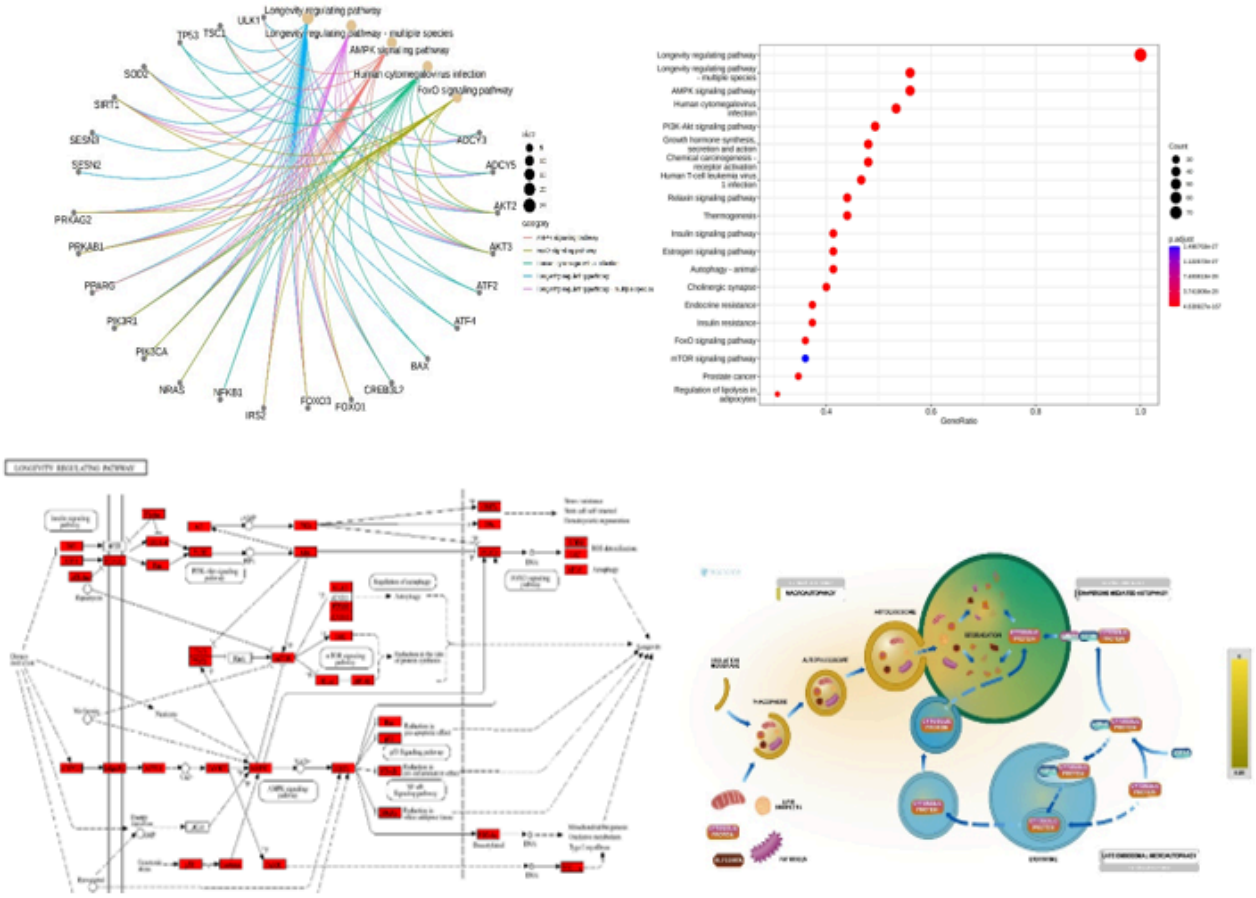

Figure 2

Significant gene pathway network enrichment mapping, KEGG and Reactome for longevity regulation pathways using STRING2.0, INPUT2.0, ShinyGO0.82 and Reactome software.

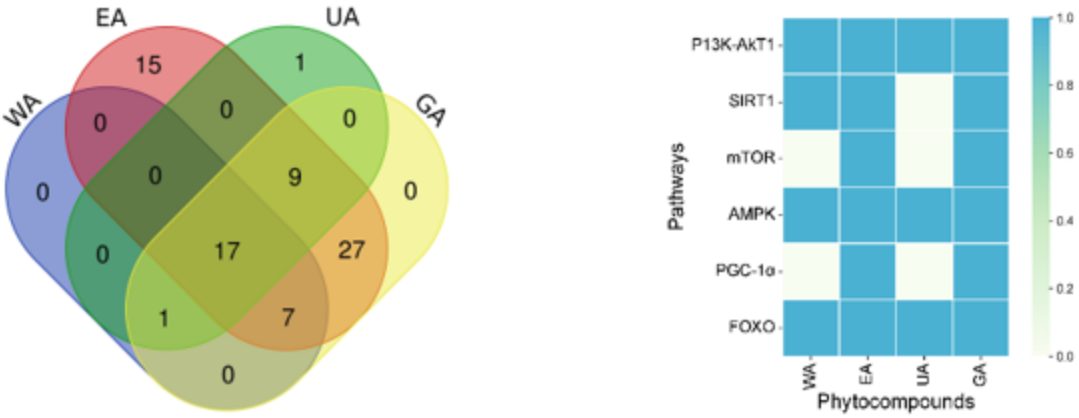

Figure 3

A schematic Venn diagram and heat map representing the significantly modulated pathways linking to regulating longevity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- LCMSCONDITIONSPhytoceeInsilicopaper.docx
- GraphicalAbstract.docx