Poster Presentation

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Statistics regarding particle interactions in granular material of high density in conditions of uniaxial compression

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There is a close correlation between how stress evolves in material characterised by high density and granularity and contacting particle interactions. Statistics associated with particle interactions and the relation of averaged local relative motion with macroscopic motion are explored. This involves assessment of how valid the Voigt and Reuss assumptions are, suggestion of how these assumptions can be extended, and exploration of effects of history in the dense granular material. Three-dimensional quantitative simulations of dense granular media subjected to uniaxial cyclical compression are used to derive the necessary statistical samples. According to outcomes, normal inter-particle forces are the main source of stresses, while inter-particle frictional tangential forces do not contribute directly to a significant extent. Nevertheless, the particle contact time is markedly increased by tangential friction, leading to a reduction in contact breakage rate. There is evidence that the rate of contact breakage represents a stress relaxation rate, and consequently, the extended relaxation time causes a considerable increase in stress with inter-particle friction.

Speaker Biography

Saleh Mohammed Alamri completed his Master's Degree in Pharmaceutical Biotechnology from De Montfort University, UK in 2014. He is currently working as an Assistant Director of Pharmacy for Material Management in Prince Sultan Military Medical City, KSA. He has presented his works in several National and International Conferences and Meetings.

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Telomere dynamics in aging

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Preservation of basic genomic stability is hallmark of the survival of a living cell. Nuclear eukar-yotic genome constitutes a specific chromosome number and their defined morphology. Telo-meres, the physical ends of the linear chromosomes protect their morphology against degradation and through preventing fusion with other chromosomes or chromosome segments. These protec-tive caps comprise of a specific repetitive DNA sequence which does not code for any protein. Shortening of telomere length occurs with the dividing human cells while the telomerase enzyme complex adds the telomeric repeat de novo, thereby assuring the genomic stability. Enormous volume of research has established an association between the shortening of telomere length, and human diseases and aging. Decreased activity of telomerase and resultant shortening of telomere lengths in aged human being and in a few animal, models have led to infer telomere length as a biomarker of aging. Such studies have, however, not been able to conclude whether telomere shortening is the cause of aging or merely a consequence. Present review explores the mechanistic aspects of telomere biology.

Speaker Biography

Asefa K Ansari did her PhD in 1984 from University of Reading, England. At present, she is settled in Chicago, USA and serving as a Director of Basic Sciences at North West Suburban Col-lege. She has thirty-seven research publications in National and International Journals and thirty-five years of teaching and research experience. Basically, she is an Entomologist. But recently, she has developed a passion for Human Genetics.

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KATP channels openers are capable of brain mitochondria KATP channel opening on nanomolar scale independent of MgATPase activity

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In CNS mitochondrial KATP channel (mKATP channel) is a promising target for the protection of neurons under metabolic stress conditions. While it is generally assumed that pharmacological mKATP channels openers (KCOs) require MgATPase activity for mKATP channel opening, literary data regarding this issue are controversial. Thus, we studied the effect of most used KCOs, diazoxide and pinacidil, on mKATP channel activity in isolated brain mitochondria in the absence and the presence of MgATP. Using light scattering technique, we obtained strong evidence that MgATP complex is dispensable for mKATP channel activation by KCOs and established high sensitivity of brain mKATP channel to these openers with full activation at <0.5 μM of KCOs. Neither Mg^{2+}, nor ATP alone affected the channels affinity to the drugs, but MgATP shifted it to conventional micromolar concentrations. To assure full channel activation, it was specifically blocked by MgATP with consequent activation by KCOs in micromolar range. The blocking of the activated channel by glibenclamide and 5-hydroxydecanoate gave the same estimate of maximal channel activity proving KCOs' ability to elicit full activation on nanomolar scale without MgATP. Based on our experiments we came to the following conclusions: 1) native KATP channels of brain mitochondria are highly sensitive to diazoxide and pinacidil, which open KATP channel independent of MgATPase activity on nanomolar concentration scale; 2) neither Mg^{2+}, nor ATP alone affected the mKATP channels affinity to KATP channels openers, but the presence of MgATP shifted it to much higher micromolar concentrations of the drugs; 3) native brain mKATP channel might comprise the sites with high affinity to diazoxide and pinacidil screened by the binding of MgATP. Obtained results indicate novel common features in the mechanism of native mKATP channel activation by pharmacological openers that would help bring new insight into understanding of mKATP channel properties.

Speaker Biography

Olga V Akopova has completed her PhD in 1997 and a Doctor of Sciences Degree in Biochemistry in 2016. Now she is a principal investigator at Circulation department of AA Bogomoletz Institute of Physiology, Ukraine. Research interests: mitochondrial potassium transport; the impact of K^+ transport on mitochondrial bioenergetics and metabolism; mKATP channels, their properties and cell-specific functions. She published a number of well cited research works devoted to the study of bioenergetic and functional effects of mKATP channel opening in brain and liver mitochondria. At present her interest is focused on the study of pharmacological properties of mKATP channels and their interactions with physiological ligands. She is the author of about 35 research works indexed in MEDLINE and Scopus databases.

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Correlation between Serum Vitamin D concentration status and Matrix Metalloproteinase-9 in patients undergoing Elective Percutaneous Coronary Intervention

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Backgrounds: Cardiovascular diseases (CVD) including atherosclerosis and coronary artery diseases (CAD) have become increasingly threatening to people's lives during recent decades. Several studies have shown that matrix metalloproteinase-9 (MMP-9) plays an important role in the process of atherosclerosis and heart remodeling and it has been suggested that higher MMP-9 levels are associated with higher risk of CVD. On the other hand, Vitamin -D deficiency have been recognized as a risk factor for CAD. According to the prevalence of vitamin D deficiency in our country, Iran, we aimed to evaluate the relationship between vitamin D status and the level of MMP-9 in patients undergoing percutaneous coronary intervention (PCI).

Methods: In this prospective cross-sectional study, patients who were candidates for elective coronary intervention were included. Baseline serum MMP-9 and vitamin D levels were measured. Patients were categorized into three groups according to their vitamin D serum level: Vitamin D-severely deficient (≤ 10 ng/ml), vitamin D-moderately deficient (11-20 ng/ml), and vitamin D-insufficient/sufficient (> 21 ng/ml).

Results: Totally, 150 patients were assessed for the serum level of MMP-9 and vitamin-D. The analysis showed that serum MMP-9 levels were higher in patients with lower vitamin-D concentrations. A significant inverse correlation was found between MMP-9 concentration and 25(OH) vitamin D level (P = 0.039).

Discussion: It may be concluded that low vitamin D level may lead to more vulnerable plaques and consequently more cardiovascular adverse effect in post-PCI patients.

Speaker Biography

Mahtabalsadat Mirjalili is currently working as a Junior Clinical Pharmacy Resident in Shiraz University of Medical Sciences, Iran. She has completed Doctor of Pharmacy from Shahid Sadoughi University of Medical Sciences, Iran. Her research works focus on antibiotic therapy and intensive care unit. She has published her research works in several National and International Conferences as well as in several reputed Journals.

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Gut motility, transit and pH: How different are we?

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Small intestine (SI) motility, transit times and pH can have implications on the absorption of poorly soluble drugs. Utilizing novel approaches, we investigated these physiological parameters in humans. The small bowel video capsule endoscope (VCE) allows visualization of the entire SI and the wireless motility capsule (SmartPill™, Medtronic, Minneapolis, MN) houses sensors that provide real-time measurements of temperature, pressure and pH of the immediate gastrointestinal (GI) luminal environment. Our findings illustrate that in some healthy subjects, pH in the proximal SI does not rise uniformly but is characterized by large fluctuations. In a third of healthy subjects, the pHmedian was 6.0 (5th, 95th percentiles 3.09, 7.06) and fluctuated over a mean period of 28 min. These pH changes can have implications on the supersaturation and precipitation of weakly basic drugs. Large inter-individual variability in the frequency of pressure activity (Ct) and area under the pressure curve (AUC) is observed in the proximal SI of healthy subjects and patients with constipation. Median AUC was 3996 mmHg s−1 (5th, 95th percentiles 948, 16866 mmHg s−1) in these two populations combined. An inverse correlation was observed between AUC and small intestinal transit times (SITT) at r=−0.49, $p < 1\times10-6$, that is a moderate correlation suggesting longer SITT with lower pressure activity. The inter-individual variations in SI pressure activity may have implications on the disintegration/dissolution of oral modified release (MR) dosage forms. The median SITT of human subjects as determined using VCE was 208 min, with times ranging from 50 to 460 min. This large inter-subject variability in transit times may explain the variability in bioavailability observed from some MR preparations. Our improved understanding of GI transit times, pH and pressure activities can be utilized in in silico and in vitro drug release and absorption models for oral drug delivery systems.

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Outcomes of integrating smart phrase interface technology to improve cancer symptom management

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Purpose: Using default's collaborative translational research model, this study's goal is to integrate, evaluate, and sustain, an evidence-based user- friendly smart phrase embedded into the emr to improve remote symptom management by cuing telephone triage nurses' assessments in a comprehensive cancer institute.

Background/significance: Managing cancer symptoms is challenging for frontline tele-triage nurses to get patients to the most appropriate levels of care. Earliest descriptive studies indicate that toggling multiple emr screens to assess toxicity risk while providing emotional support over the phone to vulnerable patients may cause missed communications, error, and dissatisfaction. Smart phrase technology to improve symptom management is not widely used nor outcome tested. This study aims to test a tele-smart phrase-emr interface to improve nurse-sensitive patient outcomes and nurse satisfaction.

Methods: Repeated-measures design will compare nurse-sensitive quality variables along a 5-point pre/post implementation trajectory in a multi-site cancer institute serving 14,000 patients. Outcome data from outpatient oncology satisfaction surveys include: managing chemotherapy side effects, education for fatigue management, appetite loss, and emotional needs met, home-based education, pain control, and perceived safety/security. LifeChat epic databases will measure nurse-sensitive changes in er visits and appointments within 24 hours. 375 tele-triaged calls at each of 5 data-collection points will be analyzed using generalized linear mixed models to construct hierarchical regressions to model outcomes. Changes in nurse satisfaction and usability will also be tested.

Conclusions/implications: Integrating smart phrase tele-emr-interface well-embedded in practice, documented in the emr, highly reliable, & widely disseminated holds promise for improving assessment to reduce treatment toxicity risk, optimize symptom management, and quantify the impact of patient engagement on quality/safety.

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Mining the serum proteome for non-invasive monitoring of kidney allograft rejection

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Introduction: We hypothesized that protein biomarkers released from rejecting allograft tissues can be detected early in the systemic circulation.

Approach: We outline our modifications in the on-going search for biomarker panel that could accurately predict complications during kidney allograft rejection. In order to increase validity of identified allograft rejection-specific biomarkers, we used high-throughput protein array platforms and applied Systems Biology approach.

Methods: Serum samples were collected prospectively from 4 groups of patients (n=25 in each group); Group 1: recipients of kidney transplant requiring kidney biopsy for renal dysfunction, Group 2: transplant recipients with stable function, Group 3: chronic kidney disease patients awaiting transplant, and Group 4: healthy individuals. Serum was labelled with the fluorescent dye Cy3 and assayed on phosphoprotein microarray platform from Full moon Biosystems. For subsequent validation by quantitative Reverse Capture Protein Microarray platform, we used individual serum samples that were spotted in serial dilutions on a glass slide and probed with the specific antibodies for predicted biomarker proteins and correlated with the severity of the disease.

Results: Using bioinformatics algorithms, we were able to identify multiple candidate graft rejection-specific biomarkers. Lower levels of Ubiquitin, p38MAPK, histone H3.1 and Tak1 and higher levels of ATM, p38MAPK, HDAC8, SAPK/JNK, GSK3a-b, NFkappa B and RelB pointing to an altered p53 Signaling pathway were associated with group 3 and group 1 patient serum. Among the tested phosphorylated proteins, phospho-species of SAPK/JNK and RelB were elevated in group 2 vs. group 3 and group 1.

Conclusion: Data suggested that these novel analytes in the serum, together or independently, may constitute a robust and quantitative serum proteomic signature for rejection of renal allografts. We conclude that detection of allograft rejection by affinity proteomics offers a promising non-invasive tool for the surveillance and early detection of kidney allograft rejection.

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Critical care patient's perspective of stress

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Background: More than 5.7 million patients are admitted annually to intensive care units (ICU) in the United States (US). Critical care hospitalization may trigger stressful experiences.

Objectives: To explore the patient's perspective of stress according to their medical diagnosis in intensive care units (ICU) and describe their perspective on stress management strategies.

Methods: A descriptive correlational design. The sample included 63 patients. The environmental stressors questionnaire (esq) was used to measure the patient's stress.

Results: Gastrointestinal (Gi) patients reported the highest mean stress score in ICU (mean=87.91), followed by sepsis cases (mean=85.67), then oncology patient's (mean=85), diabetic ketoacidosis (mean= 84.67). Orthopedic cases (mean=81.5), cardiac cases (mean=76.23), neurological (mean= 71.4), and the minimum stress score was reported by respiratory cases (mean=71). Gi patient's recommended informing them about the waiting time for any biopsy results if any, limit npo status time frame, manage pain, nausea and vomiting episodes more effectively. The remaining sepsis, oncology, dka, orthopedic and cardiac patient's recommended decreasing cardiac alarm's sound threshold, decrease blood withdrawal for lab tests, and allow family members to be at the bedside.

Conclusion: The findings may be useful for guiding interventions to provide holistic patient care that decrease the patient's stress according to their medical diagnosis

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Mechanistic modeling: the pathway to precision medicine

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There is a growing and critical need for integrating molecular systems science with computation to model complex disease processes for accelerating drug discovery, drug repurposing, validation of complementary and alternative medicine (CAM) therapies, and identification of efficacious multi-combination therapeutics, while ensuring a personalized and precise medicine. Such needs cannot be advanced without collaborative integration of knowledge across biological disciplines. This talk will share the recent successes, through multiple case studies, in the use of CytoSolve, a computational systems biology collaboratory, developed at MIT., that provides an integrative approach to address these critical needs. Previous approaches, largely based on statistical techniques, have been unscalable and largely useless to scientists who seek to understand complex biological mechanisms. CytoSolve's successes have been published in peer-reviewed journals and have received recognition in Nature for its potential to develop multi-combination therapies. These successes including: FDA allowance for a multi-combination pancreatic cancer therapeutic; the Department of Defense (DoD) and the United States Pharmacopeia (USP) understanding of toxicity and adverse reaction multi-combination nutritional supplements; and, modeling of rare diseases in orphan drug domains such as Neuromyelitis Optica (NMO) and Hereditary Angioedema (HAE) have inspired major nutraceutical researchers, cancer centers such as MD Anderson, National Cancer Institute and others to explore the use of CytoSolve for integrating CytoSolve's collaboratory with modern in vitro and in vivo methods to accelerate the development of multicombination therapeutics. This talk that will provide an introduction to a disruptive platform that will likely revolutionize development of therapeutics in the 21st century.

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Effect of electrostatics on pharmaceutical powders

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Electrostatic charging via tribocharging refers to the process of charging or electrification of two solid surfaces brought into contact and separated. In pharmaceutical manufacturing and other powder handling processes, particle charging is often a nuisance and can cause problems during manufacturing such as poor powder flow, jamming, segregation, dose inhomogeneity and even dust explosion. In this project, systematic experiments and multi-scale (quantum, particle, device scale) numerical models are performed to develop a unified theory of the relation of particle size, work function difference, and surface water adsorption to the electrostatic charging and flow behavior in granular materials. Bipolar charging is also investigated, which is a special class of tribocharging where granular materials procure two opposite polarities on different sized particles of the same material. This is vital to better understand the fundamentals of granular tribocharging and apply the derived rules to better design and optimize the powder handling equipment used in pharmaceutical industry.

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Identifying a microRNA fingerprint to predict QT prolongation

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Torsade de pointes (TdP) is a ventricular arrhythmia associated with QT interval prolongation that can be induced by several drugs. The objective was to identify circulating microRNA (miR) as potential biomarkers for risk stratification of susceptibility to QT interval prolongation. In a single center cohort study, whole blood was collected from 58 patients with coronary artery disease. Corrected QT intervals were measured by Fridericia's method (QTc). Patients were categorized according to QTc risk. Genome-wide next generation miR sequencing was performed. Multivariate regression analysis (additive model) was used to predict miRs associated with QTc risk. MiRs associated with QT interval risk were further assessed for potential functional significance using TargetScan with a context score < -0.4. 320 miRs were identified and 16 miRs were associated with QTc interval risk from the multivariate analysis ($p<0.05$; Figure). 11 of those miRs were previously related to cardiovascular function. Target scan analysis revealed 3 of the miRs may regulate cardiac ion channel gene targets associated with QTc prolongation. A profile of circulating miR has been identified that correlated with QT prolongation. The potential for a miR fingerprint to predict the susceptibility to drug induced QT prolongation warrants further investigation.

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Oral peptide delivery by a novel lipid-based system

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Bioavailability of peptide drugs is very low after oral administration. Only very few products are on the market, like immunosuppressive cyclosporine A (Sandimmun Neoral®) or antidiuretic desmospressin (Minirin®). Most other peptide drugs are given by i.v or s.c. injection of peptide solutions, s.c. administration of drug loaded polymeric implants or microparticles or by nasal administration.

In the present study we developed a liposomal system based on a combination of standard lipids and membrane spanning tetraether lipids, which are extremely stable biomolecules. The shape of the liposomes was characterized by light scattering and electron microscopy. Liposomes had an average diameter of 200-250 nm. The absorption behavior was studied in vivo in rats in absence and presence of various absorption enhancers (cetylpyridinium chloride, phenylpiperazin, sodium caprate). The liposomes containing tetraether lipids resulted in a significantly increased absorption compared to the compound alone or standard liposomes. The bioavailability of several model peptides including the cyclic octapeptide octreotide (Sandostatin®) and human growth hormone (hGH) was determined after administration of peptide loaded liposomes to rats via gavage. Blood samples were taken, and the plasma concentration of absorbed peptide was determined by specific radioimmunoassays. The absolute bioavailability (BA) of octreotide was increased by a factor of 25-30 after administration of tetraether lipid liposomes, the BA of hGH was increased by a factor of 360, indicating that formulation in such liposomes is a feasible approach to increase the bioavailability of peptide drugs after oral administration. The formulation can be further optimized by incorporation of the liposomes into a jelly matrix, thus generating a semi-solid dosage form, from which liposomes can be released in the GI-tract without loss of shape and loading capacity.

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Methacrylated chitosan with improved mucoadhesiveness for transmucosal application

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Background: The continued relevance and biomedical application of chitosan are due to its safety and mucoadhesiveness. Mucoadhesive delivery systems are desirable to extend the bladder residence time of loaded drugs. In recent years, maleimide and acrylate-functionalised delivery systems are being explored for transmucosal application due to their superior mucoadhesive features relative to thiolated drug carriers. Methacrylated drug carriers have not been explored for enhanced mucoadhesiveness. In this work we have synthesised methacrylated chitosan with a variable degree of modification (LMeCHI and HMeCHI) and evaluated their pH sensitivity, mucoadhesiveness, and safety in comparison to chitosan (CHI), for intravesical use.

Methods: Products were characterised using 1H Nuclear Magnetic Resonance (1H NMR), Fourier Transform- Infrared and UV-Vis spectroscopy. 1H NMR and ninhydrin test quantified the methacrylate grafting density on chitosan. Turbidimetric analysis of samples evaluated their resistance to pH changes in the biological fluid. The mucoadhesiveness of fluorescein sodium in the presence of the mucoadhesive polymers was evaluated using artificial urine flow-through techniques and fluorescence microscopy. MTT assay was used to study their UMUC3 malignant cell antiproliferative features.

Results: There was a broad correlation in the methacrylation extent of LMeCHI and HMeCHI obtained with both methods. Turbidimetric analysis (λ = 400 nm) revealed that the turbidity of HMeCHI solution remained unchanged from pH 3 to 9 while that of CHI and LMeCHI increased rapidly after pH 6, inferring that the stability of the drug carriers in biological fluid may be improved by methacrylation. The degree of methacrylate conjugation had a profound influence on their mucoadhesiveness. The polymers are presented in order of increasing mucoadhesion: FITC-Dextran < FS/CHI< FS/LMeCHI < FS/HMeCHI. Based on MTT assay, the UMUC3 cell antiproliferative effect of the unmodified and modified chitosan solutions (6.25-200 µg mL-1) was not significantly different, confirming the biocompatibility of our novel mucoadhesive polymers. Methacrylation of chitosan did not compromise its biocompatibility with bladder cancer cells.

Conclusions: Methacrylated chitosan is a safe drug carrier for intravesical delivery with superior mucoadhesiveness relative to chitosan. This result suggested that the degree of methacrylation can be tailored for desirable physicochemical properties of methacrylated chitosan. HMeCHI appears the most promising for intravesical delivery of bladder cancer chemotherapeutics

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Hepatoprotective effect of Achyranthes Aspera extract on non-alcoholic fatty liver in mice

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Non-alcoholic fatty liver disease is a common disease with accumulation of liver fat, and it occurs without the history of alcohol consumption, which has the same characteristics as alcoholic fatty liver and histologic findings. The aim of this study was to determine whether administration of Achyranthes aspera extracts (AAE) prevents diet induced nonalcoholic fatty liver disease. Male C57BL/6 mice (7 weeks old; initial weight 22.3 g) were randomly assigned into two groups after a 1-week adaptation period: normal control diet (CTL group) and high fat diet (HF group). CTL group and HF group freely received normal control diet and high fat diet respectively. After 12 weeks adaptation period, the HF group were assigned randomly to two groups and further fed an HFD (HF group) or an HFD supplemented with AAE (A500 group). After 4 weeks, we evaluated the body weight, serum metabolic parameters, and expression of mRNAs related to hepatic fatty acid uptake and de novo lipogenesis. The HF group exhibited higher weight gain throughout the body and liver than the CTL and A500 groups did. The HF group also showed greater expression of LXRα, LXRβ, SREBP1c, SREBP2, and C/EBPα mRNAs in the liver than the CTL and/or A500 groups. In addition, expression of ACC1, FAS, and SCD-1 mRNA in the liver were reduced, while expression of PPARγ mRNA was lower in the A500 group than in the HF group. Hepatic expression of p-AMPK/AMPK was higher in the A500 group than in the HF group. Accordingly, AAE prevents anti-inflammatory, anti-obesity and ameliorative liver fatty degeneration effects. This study provides novel information concerning the protective effect of AAE supplementation against obesity-induced nonalcoholic fatty liver disease.

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