Journal of Advanced Zoology

ISSN: 0253-7214
*Volume **44** Issue **S-5 Year 2023** Page **1777:1784***

Lipid-Based Nano-Formulation Development to Enhance Oral Bioavailability of Weakly Aqueous-Soluble Drug for Obesity and Hypertension

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Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 02 Nov 2023

Abstract

The most practical method of drug delivery is oral administration because it has a high rate of patient compliance. However, there are significant obstacles to effective oral medication delivery, including low drug enzymatic/metabolic stability and poor water solubility. Especially in the development of drug formulations for the treatment of obesity and hypertension. This research article aims to formulate solid lipid nanoparticles (SLN) of Fucoxanthin and Ramipril by the emulsification and ultrasonication methods. The nanoparticles size, polydispersity index, and the zeta potential, among other parameters, were computed. In addition, FT-IR analysis of compatibility tests between the SLNs and the loaded drug and in vitro drug release experiments were carried out. Lipid-based nano preparations have drawn plenty of interest as efficient vehicles to increase the oral bioavailability of these kinds of medications. We observed that lipid nanoparticles, have enhanced the oral bioavailability of poorly water-soluble drugs used for obesity and hypertension. Provided the above information, formulated SLNs should be further investigated using cutting-edge scientific methodologies to improve its bioavailability.

Keywords: *Hypertension, Obesity, Lipids based Nano formulation, Solid lipid nanoparticles.*

1. Introduction

Oral drug delivery is the most frequent, practical, and widely utilised mode of administration since it offers benefits including painless administration, no help, and patient compliance in comparison to other methods like, intravenous, rectal, and transdermal [1]. However, because to their poor oral absorption and bioavailability, several drugs are ineffective and fail in research and development. Poor oral bioavailability prevents several medications from achieving the minimal effective concentration necessary for therapeutic action [2]. Obesity and hypertension are two prevalent chronic diseases that pose significant health risks worldwide. The most common cause of hypertension is vascular ageing, which is increased in people with obesity [3]. Increased neurohormonal and humoral activity is observed

in obese patients [4,5]. Adipokine activity cause increased renin-angiotensin aldosterone activity in obese people. Ineffective vasodilation, decreased natriuresis, amplified sodium reabsorption via the kidney, and volume expansion are all consequences of obesity, which further contributes to high blood pressure. Pharmaceutical intervention plays a crucial role in the management of these conditions, with oral drug delivery being the most preferred and convenient route of administration [6]. However, a major hurdle in formulating effective medications for obesity and hypertension lies in the poor oral bioavailability of poorly water-soluble drugs. Poorly water-soluble drugs, characterized by low aqueous solubility and high lipophilicity, often exhibit limited dissolution and absorption in the gastrointestinal tract. As a result, their therapeutic efficacy is compromised, necessitating the development of innovative strategies to enhance their oral bioavailability. Recently, lipid-based nano formulations have shown promise for improving the oral delivery of medications that aren't highly water-soluble. Solid lipid nanoparticles (SLNs) are spherical particles with diameters ranging from 1 to 1000 nm. They serve as an alternative carrier system to conventional colloidal carriers like liposomes, nano crystals, polymeric micro, and nanoparticles emulsions [7,8]. Our team has previously stated that most natural products provide an intriguing promise for the successful treatment of a variety of disorders due to their anti-inflammatory, antioxidant, anti-diabetic, hypolipidemic, and neuroprotective qualities that have been induced by decreasing the activity of essential regulatory enzymes [9–18]. Numerous therapeutic benefits of organic substances and nanoparticles have been described in the past to regulate the negative pathophysiological consequences associated with oxidative stress, infection by microbes, gastric ulcer, hypercholesterolemia, cancer and brain diseases [19–29]. Several reports suggested their beneficial role for neurological disorders, tumours, and other diseases [30–47].

This paper provides a thorough process for creating solid lipid nanoparticles with the goal of increasing the oral bioavailability of medications that are poorly soluble in water, Fucoxanthin, an edible brown seaweed is a marine carotenoid and Ramipril is a well-known anti-hypertensive drug with potential therapeutic effects against obesity and hypertension respectively, both drugs face challenges related to their low solubility and limited oral bioavailability. Lipid-based nano formulations, such as SLNs, provide a viable means of improving medication absorption, stability, and solubility while overcoming these constraints. The main phases in the formulation development process, such as pre-formulation research, formulation design, optimisation, and characterisation methods, are described in this approach. It also emphasises how crucial it is to do in vitro research in order to evaluate the effectiveness of the nano formulation with regard to drug release, permeability, pharmacokinetics, and therapeutic efficacy. The methodology presented here serves as a guide for researchers in the field of pharmaceutical sciences to develop effective lipid-based nano formulations for enhancing oral bioavailability of poorly water-soluble drugs, particularly for the treatment of obesity and hypertension.

Over the past several decades, obesity has become a serious global problem. The accumulation of additional body fat causes obesity, a complex, multidimensional disorder that has a negative influence on one's health. The World Health Organization (WHO) reports that since 1975 [48], the prevalence of obesity has considerably increased worldwide. In 2016, there were more than 1.9 billion overweight adults. Of them, 650 million people had obesity. [49]. Having excessive fat in human body alters the human behaviour. We are aware that fat deposits cause metabolic changes linked to an elevated proinflammatory state, which disturbs body haemostasis and may impede immune responses [50,51]. Having too much body fat raises your risk of developing diabetes and heart disease [52]. In turn, the link between hypertension and many of the cardiometabolic effects of fat is reciprocal [53]. Consequently, individuals with obesity have higher incidences of hypertension than people of normal weight [54]. The pathophysiologic characteristics of adipose tissue affect sodium processing, liver and kidney function, vascular behaviour, and blood pressure levels, complicating medical treatment for hypertension [55].

Obesity-associated hypertension is induced by several linked pathophysiologic processes. The most common cause of hypertension is vascular ageing, which is increased in people who are obese [56,57]. Increased neurohormonal and humoral activity is observed in obese patients [58,59]. In obese individuals, renin-angiotensin-aldosterone system activity is elevated due to adipokine activity. Obesity has several negative effects, including ineffective vasodilation, increased renal reabsorption of salt, reduced natriuresis, and volume expansion, all of which raise the risk of high blood pressure. [60,61]. There are still many unsolved concerns regarding how the various illnesses linked to excessive mass gain interacted to develop heart and vascular related disorders including renal disorders, even though obesity is becoming more and more recognised as a severe health issue.

2. Materials And Methods

Materials

Precirol ATO and Gelucire 50/13 were purchased from Gattefossé, Palmitic Acid from Central Drug House, Fucoxanthin from Indena Pvt. Ltd, Ramipril from Cipla Ltd and Tween 80 from Croda Company. All the solvents used were in the analytical grade.

Synthesis of solid lipid nano formulations of Fucoxanthin and Ramipril

Emulsification and ultrasonication techniques were used for generating SLNs. In a nutshell, the lipid phase was melted with heating it to a temperature that was 10 ℃ over the melting points, using 10 mg palmitic acid, 50 mg Precirol ATO 5, and 20 mg Gelucire 50/13 as the starting materials. The drug (Fucoxanthin/Ramipril) weighing about 5 mg was then spread in the hot, molten lipid phase, after which the lipid phase was then given final coating of the warmed aqueous mixture containing 25 mg Tween 80. Finally, a formulation was produced utilising a probe sonicator for five minutes and a hot plate to keep the temperature constant. The finished SLNs nano formulation was lyophilized using a freeze-dryer and kept at 4 ℃ after being cooled down in ice for 30 minutes.

Characterization of SLRNs physicochemical

Zeta potential, polydispersity index (PDI), and particle size measurements

After dissolving SLN formulations in distilled water, they were agitated for five minutes. Dynamic light scattering was then used to compute the mean nanoparticle size and the polydispersity index (PDI) after the zeta potential was collected using an ELSZ-1000 zeta potential and particle size analysers. The measurements for each formulation were done in triplicate.

Colorimetry of differential scanning (DSC)

The physical condition of SLN formulations was determined using a PerkinElmer DSC 8500. Samples of drug-loaded SLNs (2 mg each), drug, blank SLNs, palmitic acid, and preciprol ATO 5 were all put individually on an aluminium pan and sealed hermetically. It was speaking of empty pots. The studies were conducted at a temperature range of 20–220 °C with a dry nitrogen gas flow rate of 50 mL/min. Ten, 2.5, and 0.2 °C/min were used as scan rates.

FT-IR Spectral analysis

The intermolecular contacts between the SLNs and the loaded medication were examined by FT-IR analysis on lyophilized blank SLNs, SLRNs (Ramipril), SLFNs (Fucoxanthin). The FT-IR spectra were collected at a resolution of 2 cm^{-1} and at a wavelength range of 500-4000 cm^{-1}.

Evaluation of loading capacity (LC) and encapsulation efficiency (EE)

A 0.5 mL centrifugal Amicon® filter tube was filled with 500 µL of diluted SLN formulation using an Eppendorf centrifuge. The drug-loaded SLNs and free drug were separated as they went through the filter by the centrifuge, which was operated for 30 minutes at 4°C and 14,000 rpm. The quantity of free medication in the supernatant was then calculated using HPLC. The EE and LC of SLNs were computed using the following equations:

$$\mathbf{EE\% = TRes{-}Sdrug\ Tdrug \times 100}$$

$$\mathbf{LC\% = Tdrug\ {-}Sdrug\ TL \times 100}$$

where, Tdrug is the Overall drug content in the SLRNs, Sdrug is drug concentration and TL denotes for total mass of lipid present in the SLNs.

Invitro release studies

SLNs formulations were quantified in vitro drug release utilising the previously reported dialysis bag diffusion technique during a 24-hour period.500 µL of dispersed SLN formulations (molecular weight cutoff of 3 k Da) were added to a dialysis bag, which was then sealed at both ends. The dialysis bag was then submerged in 25 mL of release medium at 37 ℃ and vigorously shaken at 50 strokes per minute. Both the simulated gastric fluid (SGF) and the simulated intestinal fluid (SIF) with 0.5% Tween 80 were used as release media. The SGF is made up of 2 grammes of sodium chloride, 1 litre of distilled water, 7 millilitres of hydrochloric acid, and a pH buffer of 1.2. The SIF is made up of 6.8 grammes of potassium phosphate monobasic, 0.616 grammes of sodium hydroxide, 1 litre of distilled water, and pH 6.8. At predetermined intervals (0, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours), 1 mL of the release medium was removed and replaced with 1 mL of new release medium in order to maintain sink conditions. Following that, the samples were assessed using HPLC, as was previously indicated.

3. Results and Discussion

Zeta potential, polydispersity index, and particle size measurements

Table 1 presents an overview of the mean size of particles, PDI, as well as zeta potential data for SLNs. In the presence of reducing agent, lipid oxidation turns into their respective nanostructures which is mainly responsible for the size variation. The particle size may be determined using this approach by estimating random fluctuations in the intensity of light diffused from colloidal suspension.

Table 1- Physicochemical characterization of Fucoxanthin and Ramipril-loaded SLNs (mean ±S.D, n = 3)

Group	Formulation	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)	LC (%)
I	FX-SLN	100.05 ±13.74	0.25 ± 0.05	-18.06 ± 0.41	96.45 ± 2.18	3.61
II	RM-SLN	101.28 ±18.74	0.29 ± 0.03	20.69 ± 0.63	96.45 ± 2.18	3.61

Differential scanning calorimetry (DSC)

DSC thermograms of Precirol ATO 5, palmitic acid, drugs, blank SLNs and SLRNs are presented in Figure 1. The peak temperatures for the Precirol ATO 5 and palmitic acid thermograms, which correspond to the melting points of the lipids, were 59.57 ℃ and 58.85 ℃, respectively. The drug thermogram displayed a clear endothermic peak at 269 ℃, which corresponded to its high crystallinity and the conventional melting point. The absence of an endothermic peak for fucoxanthin and ramipril in the SLNs strongly suggests that the drugs were present in the SLNs in an amorphous state rather than a crystalline one. Because of the lipids' transformation into nanoparticles, the presence of surfactant, medication, and formulation additives, as well as a little alteration in the endothermic peak of palmitic acid and Precirol ATO 5 in both drug-loaded and blank SLNs.

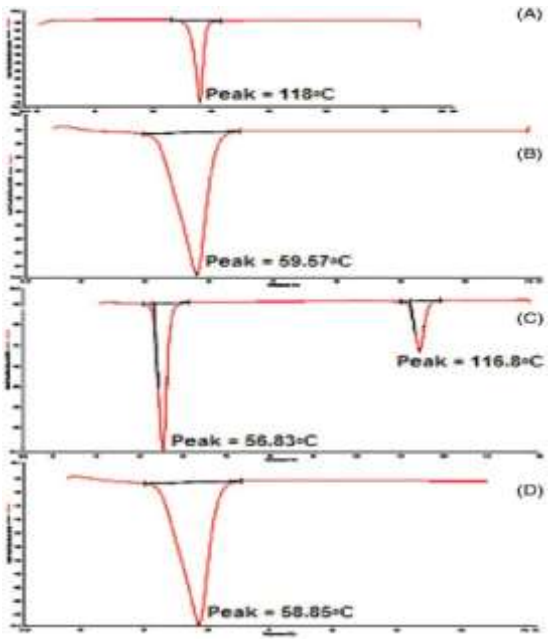

Figure 1 - DSC Thermograms of drugs and drug-loaded SLNs

FT-IR Spectral analysis

Figure 2 displays the FT-IR spectra of drugs, blank SLNs, and drug-loaded SLNs. The drug, blank SLNs, and SLRN FT-IR spectra do not show any peak shifting or drug peak loss. Drug molecular dispersion or complete entrapment within the solid lipid core of SLNs is most likely the cause of the absence of drug functional characteristic peaks from the spectra of SLRNs. Furthermore, the drug-loaded SLNs' spectra did not exhibit any additional peaks, indicating that the medication had no effect on the nature of the SLNs. Consequently, our investigation demonstrated that the medication does not interact with the solid lipid component of SLNs, indicating that the drug is suitable for SLN formulations.

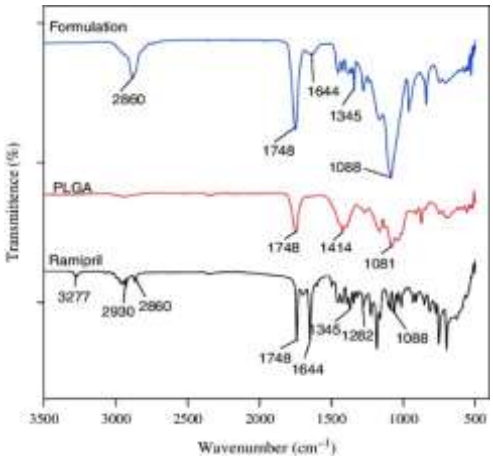

Figure 2 - FTIR of drugs, blank SLNs and drug-loaded SLNs

Evaluation of loading capacity (LC) and encapsulation efficiency (EE)

Table 1 provides the EE and LC of drug-loaded SLNs. Previous studies have shown that resveratrol may be loaded in SLNs up to 3.08% with less than 80% of EE. Because the solid lipid core of Precirol ATO 5 and palmitic acid can contain substantial quantities of both medications, Ramipril's and Fucoxanthin's high lipophilicity (octanol/water partition coefficient: Ramipril log P = 3.1 and Fucoxanthin log P = 4.5) resulted to high drug loading in the SLNs in our tests. Furthermore, the active component was maintained within the polymer mesh's core or on its surface throughout the polyelectrolyte manufacturing process. The huge cavity size of the particles' ability to encapsulate more medications is another factor.

Invitro release studies

To simulate the in vivo environment, in vitro release testing of the medicines from SLN formulations were conducted along a pH gradient that mimicked the pH in the GI tract: SGF and SIF were applied in this case. The percentage cumulative release profile of fucoxanthin and Ramipril is displayed in Figure 3. At 24 in SGF/SIF, respectively, SLNs showed an early burst release (74.48 3.72% in SGF) and a continuous release pattern (68.28 3.87% in SIF). The release rate from SLNs was higher in SGF than in SIF. Due to SLNs' burst release characteristic, it was discovered that SLNs were substantially higher in simulated stomach environment than in simulated intestinal ones.

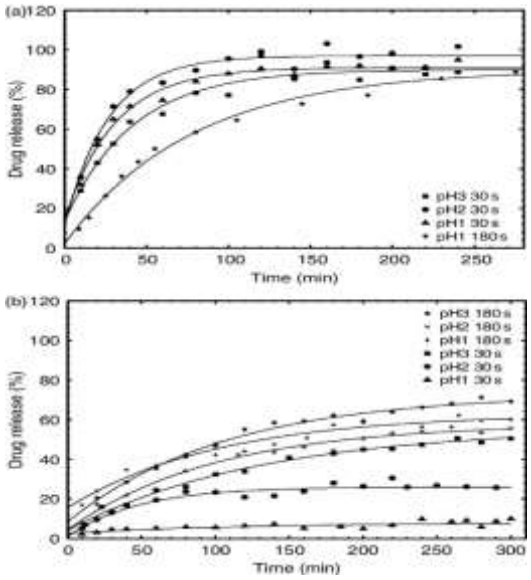

Figure 3 - Percentage Cumulative Release profile of Fucoxanthin and Ramipril SLNs

4. Conclusion

This study concludes that Lipid-based nano formulations offer a promising approach for enhancing the oral bioavailability of poorly water-soluble drugs used for obesity and hypertension. Formulated SLNs of Ramipril and Fucoxanthin upon determination of particle size showed a range of 100.05 ±13.74 nm (FX-SLN), 101.28 ±18.74 nm (RM-SLN),Thermograms of Differential scanning calorimetry (DSC) has produced a peak temperature of 59.57°C and 58.85°Cfor the Precirol ATO 5 and palmitic acid, No

peak shifting or drug peak loss is visible in the FT-IR spectra of the drug, blank SLNs, or SLRNs, concluding that there is no interaction between the medicine and the solid lipid component of SLNs, proving that the drug is appropriate for SLNs formulations. In vitro analysis demonstrated an early burst release (74.48 3.72% in SGF) and a continuous release pattern (68.28 3.87% in SIF) at 24 in SGF/SIF, based on the results, formulated SLNs of Ramipril and Fucoxanthin showed a promising increase in oral bioavailability and cutting-edge scientific methodologies must be used for further studies.

Acknowledgment

This project was supported by Scientific Research Centre at Buraydah Private Colleges under the research project (BRC-SRC/2022-002), Buraydah, Al Qassim, Kingdom of Saudi Arabia.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. Sironi AM, Gastaldelli A, Mari A, et al. Visceral fat in hypertension: influence on insulin resistance and beta-cell function. *Hypertension*. 2004;44(2):127-133. doi:10.1161/01.HYP.0000137982.10191.0a
2. Cox AJ, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol*. 2015;3(3):207-215. doi:10.1016/S2213-8587(14)70134-2
3. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114(12):1752-1761. doi:10.1172/JCI21625
4. Buglioni A, Cannone V, Cataliotti A, et al. Circulating aldosterone and natriuretic peptides in the general community: relationship to cardiorenal and metabolic disease. *Hypertension*. 2015;65(1):45-53. doi:10.1161/HYPERTENSIONAHA.114.03936
5. Gamboa A, Figueroa R, Paranjape SY, Farley G, Diedrich A, Biaggioni I. Autonomic Blockade Reverses Endothelial Dysfunction in Obesity-Associated Hypertension. *Hypertension*. 2016;68(4):1004-1010. doi:10.1161/HYPERTENSIONAHA.116.07681
6. Cassis LA, Police SB, Yiannikouris F, Thatcher SE. Local Adipose Tissue Renin-Angiotensin System. *Curr Hypertens Rep*. 2008;10(2):93-98.
7. Armario P, Calhoun DA, Oliveras A, et al. Prevalence and Clinical Characteristics of Refractory Hypertension. *J Am Heart Assoc*. 2017;6(12):e007365. doi:10.1161/JAHA.117.007365
8. Martins LC, Figueiredo VN, Quinaglia T, et al. Characteristics of resistant hypertension: ageing, body mass index, hyperaldosteronism, cardiac hypertrophy and vascular stiffness. *J Hum Hypertens*. 2011;25(9):532-538. doi:10.1038/jhh.2010.95
9. Ahmad P, Alvi SS, Iqbal D, Khan MS. Insights into pharmacological mechanisms of polydatin in targeting risk factors-mediated atherosclerosis. *Life Sci*. 2020;254:117756. doi:10.1016/j.lfs.2020.117756
10. Akhter F, Alvi SS, Ahmad P, Iqbal D, Alshehri BM, Khan MS. Therapeutic efficacy of Boerhaavia diffusa (Linn.) root methanolic extract in attenuating streptozotocin-induced diabetes, diabetes-linked hyperlipidemia and oxidative-stress in rats. *Biomedical Research and Therapy*. 2019;6(7):3293-3306. doi:10.15419/bmrat.v6i7.556
11. Alvi S, Ahmad P, Ishrat M, Iqbal D, Khan S. Secondary Metabolites from Rosemary (Rosmarinus officinalis L.): Structure, Biochemistry and Therapeutic Implications Against Neurodegenerative Diseases. In: ; 2019:1-24. doi:10.1007/978-981-13-7205-6_1
12. Alvi SS, Iqbal D, Ahmad S, Khan MS. Molecular rationale delineating the role of lycopene as a potent HMG-CoA reductase inhibitor: in vitro and in silico study. *Nat Prod Res*. 2016;30(18):2111-2114. doi:10.1080/14786419.2015.1108977
13. Iqbal D, Khan MS, Khan A, et al. In Vitro Screening for β-Hydroxy-β-methylglutaryl-CoA Reductase Inhibitory and Antioxidant Activity of Sequentially Extracted Fractions of Ficus palmata Forsk. *BioMed Research International*. 2014;2014:1-10. doi:10.1155/2014/762620
14. Iqbal D, Khan MS, Khan MS, Ahmad S, Srivastava AK. An in vitro and molecular informatics study to evaluate the antioxidative and β-hydroxy-β-methylglutaryl-CoA reductase inhibitory property of Ficus virens Ait. *Phytother Res*. 2014;28(6):899-908. doi:10.1002/ptr.5077
15. Iqbal D, Khan MS, Khan A, Ahmad S. Extenuating the role of Ficus virens Ait and its novel bioactive compound on antioxidant defense system and oxidative damage in cigarette smoke exposed rats. *Biomedical Research and Therapy*. 2016;3(07):723-732.
16. Iqbal D, Khan A, A Ansari I, Khan MS. Investigating The Role of Novel Bioactive Compound from Ficus Virens Ait on Cigarette Smoke Induced Oxidative Stress and Hyperlipidemia in Rats. *Iran J Pharm Res*. 2017;16(3):1089-1103.
17. Khatoon A, Khan F, Ahmad N, et al. Silver nanoparticles from leaf extract of Mentha piperita: Eco-friendly synthesis and effect on acetylcholinesterase activity. *Life Sci*. 2018;209:430-434. doi:10.1016/j.lfs.2018.08.046
18. Nabi R, Alvi SS, Shah A, et al. Modulatory role of HMG-CoA reductase inhibitors and ezetimibe on LDL-AGEs-induced ROS generation and RAGE-associated signalling in HEK-293 Cells. *Life Sci*. 2019;235:116823. doi:10.1016/j.lfs.2019.116823

19. Iqbal D, Khan MS, Khan A, et al. In Vitro Screening for β-Hydroxy-β-methylglutaryl-CoA Reductase Inhibitory and Antioxidant Activity of Sequentially Extracted Fractions of Ficus palmata Forsk. *BioMed Res Int*. 2014;2014:e762620. doi:10.1155/2014/762620
20. Iqbal D, Khan MS, Khan MS, Ahmad S, Srivastava AK. An in vitro and molecular informatics study to evaluate the antioxidative and β-hydroxy-β-methylglutaryl-CoA reductase inhibitory property of Ficus virens Ait. *Phytother Res*. 2014;28(6):899-908. doi:10.1002/ptr.5077
21. Iqbal D, Khan MS, Khan MS, Ahmad S, Hussain MS, Ali M. Bioactivity guided fractionation and hypolipidemic property of a novel HMG-CoA reductase inhibitor from Ficus virens Ait. *Lipids Health Dis*. 2015;14(1):15. doi:10.1186/s12944-015-0013-6
22. Iqbal D, Khan MS, Waiz M, et al. Exploring the Binding Pattern of Geraniol with Acetylcholinesterase through In Silico Docking, Molecular Dynamics Simulation, and In Vitro Enzyme Inhibition Kinetics Studies. *Cells*. 2021;10(12):3533. doi:10.3390/cells10123533
23. Ahmad J. Evaluation of Antioxidant and Antimicrobial Activity of Ficus Carica Leaves: an In Vitro Approach. *J Plant Pathol Microb*. 2012;04(01). doi:10.4172/2157-7471.1000157
24. Iqbal D, Dukhyil AB, Khan MS. Geno-Protective, Free Radical Scavenging and Antimicrobial Potential of Hyptis suaveolens Methanolic Fraction: An In-Vitro Study. *Journal of Pharmaceutical Research International*. Published online March 15, 2021:46-57. doi:10.9734/jpri/2021/v33i1131243
25. Ahmad N, Bhatnagar S, Saxena R, Iqbal D, Ghosh AK, Dutta R. Biosynthesis and characterization of gold nanoparticles: Kinetics, in vitro and in vivo study. *Mater Sci Eng C Mater Biol Appl*. 2017;78:553-564. doi:10.1016/j.msec.2017.03.282
26. Alhoqail WA, Alothaim AS, Suhail M, et al. Husk-like Zinc Oxide Nanoparticles Induce Apoptosis through ROS Generation in Epidermoid Carcinoma Cells: Effect of Incubation Period on Sol-Gel Synthesis and Anti-Cancerous Properties. *Biomedicines*. 2023;11(2):320. doi:10.3390/biomedicines11020320
27. Bano N, Iqbal D, Al Othaim A, et al. Antibacterial efficacy of synthesized silver nanoparticles of Microbacterium proteolyticum LA2(R) and Streptomyces rochei LA2(O) against biofilm forming meningitis causing microbes. *Sci Rep*. 2023;13(1):4150. doi:10.1038/s41598-023-30215-9
28. Bhattacharjee R, Negi A, Bhattacharya B, et al. Nanotheranostics to target antibiotic-resistant bacteria: Strategies and applications. *OpenNano*. Published online 2023:100138.
29. Abdel-Hadi A, Iqbal D, Alharbi R, et al. Myco-Synthesis of Silver Nanoparticles and Their Bioactive Role against Pathogenic Microbes. *Biology*. 2023;12(5):661.
30. Jangra A, Gola P, Singh J, et al. Emergence of taurine as a therapeutic agent for neurological disorders. *Neural Regeneration Research*. 2024;19(1):62. doi:10.4103/1673-5374.374139
31. Iqbal D, Rehman MT, Alajmi MF, et al. Multitargeted Virtual Screening and Molecular Simulation of Natural Product-like Compounds against GSK3β, NMDA-Receptor, and BACE-1 for the Management of Alzheimer's Disease. *Pharmaceuticals*. 2023;16(4):622.
32. Alsagaby SA, Iqbal D, Ahmad I, et al. In silico investigations identified Butyl Xanalterate to competently target CK2α (CSNK2A1) for therapy of chronic lymphocytic leukemia. *Sci Rep*. 2022;12(1):17648. doi:10.1038/s41598-022-21546-0
33. Mathur R, Jha NK, Saini G, et al. Epigenetic factors in breast cancer therapy. *Frontiers in Genetics*. 2022;13:886487-886487.
34. Mir SA, Noor M, Manzar MD, et al. Prevalence of rheumatoid arthritis and diagnostic validity of a prediction score, in patients visiting orthropedic clinics in the Madinah region of Saudi Arabia: a retrospective cross-sectional study. *PeerJ*. 2022;10:e14362. doi:10.7717/peerj.14362
35. Mani S, Jindal D, Chopra H, et al. ROCK2 inhibition: A futuristic approach for the management of Alzheimer's disease. *Neuroscience & Biobehavioral Reviews*. 2022;142:104871. doi:10.1016/j.neubiorev.2022.104871
36. Moin A, Huwaimel B, Alobaida A, et al. Dithymoquinone Analogues as Potential Candidate(s) for Neurological Manifestation Associated with COVID-19: A Therapeutic Strategy for Neuro-COVID. *Life*. 2022;12(7):1076. doi:10.3390/life12071076
37. Hussain T, Habib AH, Rafeeq MM, et al. Oleuropein as a Potent Compound against Neurological Complications Linked with COVID-19: A Computational Biology Approach. *Entropy*. 2022;24(7):881. doi:10.3390/e24070881
38. Khare N, Maheshwari SK, Rizvi SMD, et al. Homology Modelling, Molecular Docking and Molecular Dynamics Simulation Studies of CALMH1 against Secondary Metabolites of Bauhinia variegata to Treat Alzheimer's Disease. *Brain Sciences*. 2022;12(6):770. doi:10.3390/brainsci12060770
39. Jahan S, Redhu NS, Siddiqui AJ, et al. Nobiletin as a Neuroprotectant against NMDA Receptors: An In Silico Approach. *Pharmaceutics*. 2022;14(6):1123. doi:10.3390/pharmaceutics14061123
40. Jahan S, Ansari UA, Siddiqui AJ, et al. Nobiletin Ameliorates Cellular Damage and Stress Response and Restores Neuronal Identity Altered by Sodium Arsenate Exposure in Human iPSCs-Derived hNPCs. *Pharmaceuticals*. 2022;15(5):593. doi:10.3390/ph15050593
41. Iqbal D, Rizvi SMD, Rehman MT, et al. Soyasapogenol-B as a Potential Multitarget Therapeutic Agent for Neurodegenerative Disorders: Molecular Docking and Dynamics Study. *Entropy*. 2022;24(5):593. doi:10.3390/e24050593
42. Sultana S, Ali M, Mir SR, Iqbal D. Isolation and characterization of glycosides from convolvulus prostratus, ficus virens, phoenix dactifera, spondias mangifera and terminalia belerica. *Eur J Pharm Med Res*. 2018;5:310-318.

43. Bhattacharjee R, Das SS, Biswal SS, et al. Mechanistic role of HPV-associated early proteins in cervical cancer: Molecular pathways and targeted therapeutic strategies. *Critical Reviews in Oncology/Hematology*. 2022;174:103675. doi:10.1016/j.critrevonc.2022.103675
44. Bijani S, Iqbal D, Mirza S, et al. Green Synthesis and Anticancer Potential of 1,4-Dihydropyridines-Based Triazole Derivatives: In Silico and In Vitro Study. *Life*. 2022;12(4):519. doi:10.3390/life12040519
45. Goel H, Goyal K, Pandey AK, et al. Elucidations of Molecular Mechanism and Mechanistic Effects of Environmental Toxicants in Neurological Disorders. *CNS & Neurological Disorders - Drug Targets-CNS & Neurological Disorders)*. 2023;22(1):84-97. doi:10.2174/1871527321666220329103610
46. Jahan S, Mukherjee S, Ali S, et al. Pioneer role of extracellular vesicles as modulators of cancer initiation in progression, drug therapy, and vaccine prospects. *Cells*. 2022;11(3):490.
47. Iqbal D, Rehman MT, Bin Dukhyil A, et al. High-Throughput Screening and Molecular Dynamics Simulation of Natural Product-like Compounds against Alzheimer's Disease through Multitarget Approach. *Pharmaceuticals*. 2021;14(9):937. doi:10.3390/ph14090937
48. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*. 2018;319(16):1723-1725. doi:10.1001/jama.2018.3060
49. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
50. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377(9771):1085-1095. doi:10.1016/S0140-6736(11)60105-0
51. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic Burden of Obesity: A Systematic Literature Review. *Int J Environ Res Public Health*. 2017;14(4):435. doi:10.3390/ijerph14040435
52. Franceschini N, Gouskova NA, Reiner AP, et al. Adiposity Patterns and the Risk for ESRD in Postmenopausal Women. *Clinical Journal of the American Society of Nephrology*. 2015;10(2):241. doi:10.2215/CJN.02860314
53. Booth JN, Li J, Zhang L, Chen L, Muntner P, Egan B. Trends in Prehypertension and Hypertension Risk Factors in US Adults: 1999-2012. *Hypertension*. 2017;70(2):275-284. doi:10.1161/HYPERTENSIONAHA.116.09004
54. Saydah S, Bullard KM, Cheng Y, et al. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. *Obesity*. 2014;22(8):1888-1895. doi:10.1002/oby.20761
55. Cohen JB. Hypertension in Obesity and the Impact of Weight Loss. *Curr Cardiol Rep*. 2017;19(10):98. doi:10.1007/s11886-017-0912-4
56. Ahmed SB, Fisher NDL, Stevanovic R, Hollenberg NK. Body Mass Index and Angiotensin-Dependent Control of the Renal Circulation in Healthy Humans. *Hypertension*. 2005;46(6):1316-1320. doi:10.1161/01.HYP.0000190819.07663.da
57. Zuckerman M, Greller HA, Babu KM. A Review of the Toxicologic Implications of Obesity. *J Med Toxicol*. 2015;11(3):342-354. doi:10.1007/s13181-015-0488-6
58. Raij L, Egan BM, Zappe DH, Purkayastha D, Samuel R, Sowers JR. Office and ambulatory blood pressure-lowering effects of combination valsartan/hydrochlorothiazide vs. hydrochlorothiazide-based therapy in obese, hypertensive patients. *J Clin Hypertens (Greenwich)*. 2011;13(10):731-738. doi:10.1111/j.1751-7176.2011.00499.x
59. Wofford MR, Anderson DC, Brown CA, Jones DW, Miller ME, Hall JE. Antihypertensive effect of alpha- and beta-adrenergic blockade in obese and lean hypertensive subjects. *Am J Hypertens*. 2001;14(7 Pt 1):694-698. doi:10.1016/s0895-7061(01)01293-6
60. Cohen JB, Stephens-Shields AJ, Denburg MR, Anderson AH, Townsend RR, Reese PP. Obesity, Renin-Angiotensin System Blockade and Risk of Adverse Renal Outcomes: A Population-Based Cohort Study. *Am J Nephrol*. 2016;43(6):431-440. doi:10.1159/000446862
61. Schmieder RE, Philipp T, Gueredíaga J, Gorostidi M, Bush C, Keefe DL. Aliskiren-based therapy lowers blood pressure more effectively than hydrochlorothiazide-based therapy in obese patients with hypertension: sub-analysis of a 52-week, randomized, double-blind trial. *J Hypertens*. 2009;27(7):1493-1501. doi:10.1097/HJH.0b013e32832be593