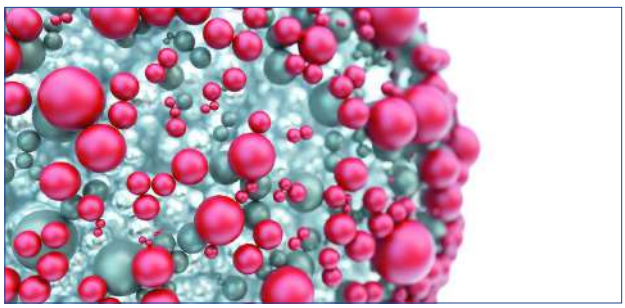
Accepted Abstracts

Pharmaceutical Science 2022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Discovery of a highly potent novel Rifampicin analog by preparing a hybrid of the precursors of the antibiotic drugs Rifampicin and Clofazimine

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Introduction: Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis (Mtb). The present work reports the design and synthesis of a hybrid of the precursors of rifampicin and clofazimine, which led to the discovery of a novel Rifaphenazine (RPZ) molecule with potent anti-TB activity.

Methods: The synthesized novel molecule was characterized using high-resolution mass spectroscopy and NMR spectroscopy. The efficacy of RPZ was evaluated in-vitro using the reference strain Mtb H37Rv. Herein, 2,3 diamino phenazine, a precursor of an anti-TB drug clofazimine, was tethered to the rifampicin core. This 2,3 diamino phenazine did not have an inherent anti-TB activity even at a concentration of up to 2 µg/mL, while rifampicin did not exhibit any activity against Mtb at a concentration of 0.1 µg/mL.

Results: The synthesized novel Rifaphenzine (RPZ) inhibited 78% of the Mtb colonies at a drug concentration of 0.1 µg/mL, while 93% of the bacterial colonies were killed at 0.5 µg/mL of the drug. Furthermore, the Minimum Inhibitory Concentration (MIC) value for RPZ was 1 µg/mL. Time-kill studies revealed that all bacterial colonies were killed within a period of 24 h. Cytotoxicity studies (IC50) were performed on human monocytic cell line THP-1, and the determined IC50 value was 96 µg/mL, which is non-cytotoxic.

Conclusion: These data suggested that Rifaphenazine (RPZ) is a promising pre-clinical candidate for the treatment of drug-susceptible tuberculosis (DS-TB). The results of the in-vitro analysis suggest that the efficacy of Mtb inhibition demonstrated by RPZ at a lower drug concentration has a prospect of shortening the TB treatment duration. The significance of the present work is that, even at a one-tenth concentration of rifampicin MIC, the drug candidate Rifaphenazine (RPZ) was able to kill 78% of Mtb, while rifampicin could kill zero percent Mtb at the same concentration.

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Isofraxidin: Synthesis, biosynthesis, isolation, pharmacokinetic and pharmacological properties

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Isofraxidin (7-hydroxy-6, 8-dimethoxy coumarin) (IF) is a hydroxy coumarin with several biological and pharmacological activities. The plant kingdom is of the most prominent sources of IF, which, among them, Eleutherococcus and Fraxinus are the well-known genera in which IF could be isolated/extracted from their species. Considering the complex pathophysiological mechanisms behind some diseases (e.g., cancer, neurodegenerative diseases, and heart diseases), introducing IF as a potent multi-target agent, which possesses several herbal sources and the multiple methods for isolation/purification/synthesis, along with the unique pharmacokinetic profile and low levels of side effects could be of great importance. Accordingly, a comprehensive review was done without time limitations until February 2020. IF extraction methods include microwave, mechanochemical, and ultrasound, along with other conventional methods in the presence of semi-polar solvents such as ethyl acetate (EtOAc). In addition to the isolation methods, related synthesis protocols of IF is also of great importance. From the synthesis point of view, benzaldehyde derivatives are widely used as precursors for IF synthesis. Along with the methods of isolation and biosynthesis, IF pharmacokinetic studies showed hopeful in vivo results of its rapid absorption after oral uses, leading to different pharmacological effects. In this regard, IF targets varieties of inflammatory mediators including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), tumor necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs). thereby indicating anticancer, cardioprotective, and neuroprotective effects. This is the first review on the synthesis, biosynthesis, isolation, and pharmacokinetic and pharmacological properties of IF in combating different diseases.

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Crosstalk mediated by Adipo-BRD7 gene therapy improves insulin resistance and improved liver and heart functions

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The most critical factor in the emergence of metabolic diseases is obesity. Malfunctioning of Adipose tissue instigates several pathophysiological conditions in the liver, kidney, and heart. BRDs are conserved protein modules that recognize acetyl-lysine motifs. BRD7 is a ubiquitously expressed 75kDa molecular weight protein, which is a member of the BRD family. BRD7 revealed in the multiple organs, including the liver, brain, heart, colon, lung, and skin, but the exact function of BRD7 is still not fully understood.

The study aimed to demonstrate the adipocyte-specific BRD7 gene therapy approach for preventing the development of obesity-induced pathophysiology of metabolic diseases. Adipocytes' specific expression of BRD7 was achieved using a lentiviral vector expressing BRD7 under the adiponectin vector (Ln-adipo- BRD7). The Mice fed a high-fat diet (HFD) developed adipocyte hypertrophy, fibrosis, increased inflammatory adipokines, decreased mitochondrial respiration, insulin resistance, vascular dysfunction, and impaired heart mitochondrial signaling. Furthermore, mice developed macrostetosis and lipid droplet hypertrophy in the liver hepatocytes. The dangerous effects prevented by the selective expression of BRD7 in adipocytes. Ln-adipose- BRD7-transfected mice on an HFD display increased cellular respiration, increased oxygen consumption, improved mitochondrial function, and decreased adipocyte size.

Moreover, PCR arrays confirmed that targeting adipocytes with BRD7overrides the genetic susceptibility of adiposopathy and correlated with restoration of anti-inflammatory, thermogenic and mitochondrial genes. Furthermore, crosstalk of adipocytes improves liver macrostetosis. Our data demonstrate that BRD-7gene therapy improved adipose tissue function and positively impacted distal organs like the liver and heart suggesting that specific targeting of BRD7 gene therapy is an attractive therapeutic approach for improving insulin sensitivity and metabolic activity and vascular function in metabolic syndrome.

Keywords: Metabolic Syndrome, BRD7, metabolism, mitochondria, type II diabetes.

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Identification of hordenine as a potential inhibitor of pyruvate dehydrogenase kinase 3

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Design and development of potential pyruvate dehydrogenase kinase 3 (PDK3) inhibitors has gained attention because of their possible therapeutic uses in lung cancer therapy. In the present study, the binding affinity of naturally occurring alkaloids, hordenine, vincamine, tryptamine, cinchonine, and colcemid was measured with PDK3. Molecular docking and fluorescence binding studies suggested that all these compounds show considerable binding affinity for PDK3. Among them, the affinity of hordenine to the PDK3 was excellent (K=106 M-1) which was further complemented by isothermal titration calorimetric measurements. Molecular docking study shows that hordenine binds in the active site pocket of PDK3 and forms a significant number of non-covalent interactions with functionally important residues. All-atom molecular dynamics (MD) simulation study suggested that the PDK3-hordenine complex is stabilized throughout the trajectory of 100ns and leads to fewer conformational changes. Enzyme inhibition studies showed that hordenine significantly inhibits the activity of PDK3 with an IC50 value of 5.4 µM. Furthermore, hordenine inhibited the proliferation of human lung cancer cells (A549 and H1299) with admirable IC50 value. In summary, our findings provide the basis for the therapeutic implication of hordenine and its derivatives in lung cancer and PDK3-related diseases after required in vivo validation.

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Awareness of COVID-19 disease among Pakistani residents during a rapid outbreak: A rapid online survey

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Background: Coronavirus disease (COVID-19) is a lethal illness that affects most countries around the world. For the design of effective control strategies during a public health crisis, public awareness, including knowledge of signs and symptoms, mode of transmission, and hygiene of COVID-19, is critical. The current research aims to examine the viewpoint of the public on COVID-19, including their perception, attitude and practices.

Methods: During the rapid outbreak of COVID-19 in Pakistan, a rapid online survey comprising 22 items was administered. Questions centered on COVID-19 prevention, transmission, clinical characteristics, and control. Besides, the participants' behaviors and activities were discussed. During data processing, descriptive statistics, Mann- Whitney tests, Kruskal- Wallis tests, and regression analysis were performed.

Results: This study included a total of 1257 respondents. Most of the respondents had good knowledge of COVID-19 (good=64.8%, average=30.5%, poor=4.7 percent). It was observed that gender, marital status, education and residence significantly associate with the information score. The overwhelming majority of survey respondents (77.0 percent) thought that COVID-19 in Pakistan would be successfully regulated. Among the participants, the activities of wearing a mask (85.8%) and handwashing (88.1%) were popular.

Conclusion: The participants demonstrated good awareness and rational attitudes and practices towards most aspects of the COVID-19 outbreak. By mass-level schooling, changes in some areas could be made.

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