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Forsythia's pharmacological evaluation and genetic toxicology

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Abstract

The primary component of Forsythia suspense, forsythin, is therapeutically used to treat fever, viral colds, gonorrhoea, and ulcers. The objective of this study was to assess the safety of forsythin for human use as well as any potential genetic harm. The Ames test, chromosomal aberration (CA) test, and bone marrow micronucleus (MN) test were used to evaluate the genetic toxicity of forsythin in vivo in accordance with GLP standards and test guidelines. In the Ames test, the number of His + revertant colonies was counted after five Salmonella typhimurium strains were subjected to varying forsythin concentrations in the presence or absence of the S9 mixture. In the CA test, chromosomal abnormalities were identified after treating Chinese hamster lung (CHL) fibroblast cells with various concentrations of forsythin, mitomycin C, or cyclophosphamide in the presence or absence of the S9 mixture. The MN test involved isolating the bone marrow from the mice that had received various treatments and calculating the ratios of polychromatic erythrocytes (PCE) and erythrocytes (PCE/(PCE + NCE)). Following the division of the beagle dogs into four groups-a negative control group, a low-dose group, a medium-dose group, and a high-dose group-a telemetry system was utilised to assess the safety of forsythin use. Results from the Ames test revealed that whether the S9 was present or not, there was no statistically dose-dependent increase in the number of colonies in any of the test strains.

When the S9 mixture was present, the number of cells with aberrations in the CHL fibroblast cells treated with low, medium, and high doses of forsythin for 24 or 48 hours was, respectively, 5.0/2.5, 4.5/1.5, and 5.0/5.0, and it was, respectively, 5.0, 5.0, and 4.5 when the S9 mixture was not present. These findings demonstrated that neither the presence (2.0) nor the absence (4.0/2.5 for 24/48 h) of the S9 combination significantly differed from the negative control group. The MN test revealed that forsythin had no cytotoxicity because the values of PCE/ (PCE + NCE) in the negative, positive controls, and forsythin treatment groups were all greater than 20%. Furthermore, the telemetry approach did not reveal any appreciable toxicological effects of forsythin on blood pressure, respiration, temperature, ECG, and other physiological indicators in the aware beagle dogs of different groups. Our results indicated that forsythin is suitable for continued development and prospective application because it has a negligible risk of genetic toxicity and no major toxicological consequences.

Keywords: Genetic toxicology; Genotoxicity; Genetic engineering; Pharmaceutical development.

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Introduction

Traditional Chinese medicine (TCM) has a long history of use in clinical settings in China. TCM has been gaining worldwide attention due to its therapeutic effects and special capacity to treat medical issues that Western pharmaceuticals are unable

to resolve. According to reports, 80% of the world's population, or about 4 billion people, use TCM for medical purposes. People have historically believed that herbal remedies are safer than conventional treatments. The effectiveness and safety of TCM need to be further researched given its popularity [1, 2].

In China, Korea, Japan, and certain European nations, Forsythia suspensa, a member of the genus Forsythia and family Oleaceae, is widely dispersed. Clinically, the TCM herb forsythia suspensa is frequently used to treat fever, viral colds, gonorrhoea, and ulcers. The primary component of Forsythia suspensa, forsythin, is a crucial indicator of the herb's quality. Previous research has demonstrated that Forsythia suspensa's leaves have larger concentrations of active ingredients than its fruits, such as forsythin, forsythiaside, and oleanolic acid. Pharmacoeconomic analysis shows that forsythin, which is isolated from Forsythia suspensa leaves, will significantly increase the medical and financial worth of this source of medicinal material. Forsythin also contains a wide range of pharmacological activities that have been noted, including antibacterial, antioxidative, antiviral, hypolipidemic, hepatoprotective, anti-inflammatory, antoxidative stress, and antiapoptotic effects. Demonstrated how forsythin might prevent the zebra fish tissue necrosis and neutrophil infiltration caused by lipopolysaccharide (LPS) by controlling the expression of inflammatory cytokines (IL-6, IL-1, and NF-kB). According to another study, forsythin mixed with autophagy inhibitors could reduce the growth of human laryngeal carcinoma epithelial cells (HEp-2 cells) and trigger their apoptosis, suggesting that this combination may be a novel approach to treating laryngeal squamous cell carcinoma. Forsythin's safety hasn't been adequately explained, though [3-6].

The genetic material that is left outside of the cell nucleus during mitotic anaphase as a result of intracellular chromosomal disruption or spindle fragmentation is known as the micronucleus. A telemetry device is also advised for usage in conscious animals because it can reduce interference from anaesthetic and animal activity restrictions and enhance the test's sensitivity for safety pharmacology parameters. Therefore, based on the Good Laboratory Practice (GLP) regulations and test guidelines set forth by the China Food and Drug Administration (CFDA) and Organization for Economic Cooperation and Development (OECD), the genetic toxicity and safe use of forsythin were investigated in this study using the Ames test, chromosomal aberrations (CA) test, bone marrow micronucleus (MN) test, and telemetry method [7].

Materials and Methods

Dalian Fusheng Pharmaceutical Co., Ltd. (Liaoning, China) supplied the forsythin (batch no. 20160401), and its purity was assessed using high performance liquid chromatography-UV (HPLC-UV), as previously mentioned. A Symmetry Shield C18 column (4.6 250 mm, 5 m, Ireland) and analytical system (Waters Corporation, MA, and USA) were employed, to put it briefly. The mobile phase was made from water and acetonitrile (V/V: 68/32) and the peak signal was found at 277 nm in wavelength. Forsythin's HPLC diagram may be found in Figure 1, and its purity was 91.61% [8].

Prior to tests, all animals were confined and acclimated for a week. Polypropylene was utilised to make the food cages for the mice studies, and they had the following dimensions: 320 mm 202 mm 135 mm. In each cage, there were 3-6 mice being fed. The animal room's ambient temperature was 20–26°C, the relative humidity was 40–70%, and the minimum ventilation rate was 15 times per hour with a 12–12 h light/dark cycle. Bedding options included corncob or poplar. For beagle dog tests, stainless steel beagle dog cages of 100 cm by 120 cm by 90 cm were used. Each dog was housed in a separate cage during the trial. The animal room had an ambient temperature of 16–26°C, a relative humidity of 40–70%, and a ventilation rate of at least 8 times per hour with 12 hours of daylight and 12 hours of darkness. Throughout the tests, all animals—including beagle dogs and ICR mice—have full access to food and water. The Guangdong Lewwin Pharmaceutical Research Institute Co., Ltd. Institutional Animal Care and Use Committee gave its approval to the experimental methods (IA-SE2016014-02 and IA-SE2016015-01). The Association for Assessment and Accreditation of Laboratory Animal Care has granted full accreditation to the Lewwin location (AAALAC) [9].

Discussion

According to the conventional "one drug, one target, one disease" paradigm, modern pharmaceuticals were initially developed for specific targets. Drugs however, sometimes show "off-target" pharmacology which could lead to unforeseen adverse effects or new therapeutic objectives. As a result, the network pharmacology model was recommended to clarify the complexity of biological interaction processes through networks involving drug-target, drug-disease, and other relationships. In this study, it is evidently observed that approved drugs tend to contact with more targets, with each of them having an average interaction potential of 3.891 targets, as reflected by differences between the approved drug-target network and the withdrawn drug-target network as reflected by multiple network topology properties [10].

While "hot" targets that are only connected by approved drugs are primarily found in the fields of antineoplastic, anti-inflammatory, and antibacterial therapies, those that are connected by both approved drugs and withdrawn drugs are found in the central and peripheral nervous systems for the treatment of conditions like depression, Parkinson's syndrome, hypertension, and arrhythmia. This finding would provide helpful direction for research intentions on specific goals taking failure risks for drugs involved into account. In light of the combined findings, it is evident that the network based method may offer important data for maintaining a balance between various targeted drug design and negative side effects, particularly in some therapeutic areas.

The two drug-target network models could also be used to forecast possible targets or pharmacovigilance for marketed medications or unknown substances based on their chemical structures when combined with 2D chemical fingerprint similarity estimates. We specifically looked into issues with drug safety brought on by natural compounds taken from well-known medicinal plants. As is well known, natural products have been instrumental in the development of chemotherapies, but for the majority of them,

neither the bioactive mechanisms nor the safety limits are well understood. Thus, mapping of natural products onto the two drug-target networks would provide more information for elucidations using structural chemical properties as mediums. Natural products from the company's internal TCM database are found to have some structural diversity (45.83% of them have Tanimoto coefficients below 0.7 compared to all drugs), which would significantly expand the chemical space. Of these, 54.17% could be chosen by chemical similarity measurements for potential pharmacovigilance explorations.

Technically speaking, the method would perform better or provide more information if 3D geometric shape measurements or other complex functions, including those using information mining of medical literature, could be taken into account for the similarity computation. In reality, it is difficult to determine how most medications interact with their active conformations. Calculating similarity values between conformation sets, which would drain processing resources and increase uncertainty, could therefore be a significant challenge. Additionally, there aren't many pharmacology studies on natural compounds readily available, which make it challenging to implement text mining techniques. Therefore, in the studies presented here, we tried to make these issues simpler by only highlighting the qualitative potential therapeutic risks of the medications.

Finally, our methods combined the benefits of network analysis and chemo informatics, which can not only uncover potential side-effect events but also reveal topology properties of targets corresponding to disease modules or pathways, in contrast to adverse drug reaction prediction methods based on sole similarity measurements, such as the well-known similarity ensemble approach (SEA). As a result, rather than focusing on a single target, it would offer comprehensive data for medication safety surveillance.

Conclusion

Drug-target data from the Drug Bank database was regularised to create drug-target networks, and network topology measurements were made to analyse them in order to find differences between approved drugs and withdrew pharmaceuticals. Particularly, connectivity-corresponding characteristics like degrees, linked component numbers, and average neighbour numbers were highlighted because they considerably distinguished one another and suggested that approved medications were generally more likely to interact with more targets. The causes for these drugs' withdrawal were then looked into, and it was discovered that every one of them had failed due to unanticipated negative effects. Additionally, 2D fingerprint similarity computations were used for approved medications and natural products from an internal TCM database for pharmacovigilance research, using the chemical structures of withdrew drugs as probes.

This strategy, particularly for substances with unclear targets or mechanisms like natural products, was found to be effective for providing medication safety indications, which is consistent with subsequent text mining from existing publications. This is the first time that network-based technologies have been utilised to concentrate and assess pharmacovigilance on natural goods on a wide scale. We think that the network technique combined with cheminformatics measurement would be very beneficial for drug safety monitoring throughout the entire drug development process.

Conflict of Interests

None

Acknowledgments

None

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