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Review

Notopterol for the Treatment of Human Disorders and Associated Secondary Complications: Concerns and Future Prospects

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Abstract

Notopterol is one of the main active phytochemical of Chinese herb *Notopterygium incisum* and *Notopterygium franchetii*. The aim of the present work is to collect all the scientific information of notopterol from different scientific databases and analyzed in the present work in order to know the health beneficial aspects of notopterol in medicine. Scientific data of notopterol has been collected in the present work from various scientific databases for its biological potential and pharmacological activities with its analytical aspects. However, detailed pharmacological activities of notopterol have also been discussed in the present paper. All the scientific data of notopterol have been collected from PubMed, Science Direct, Scopus, and Google in the present work. Presented scientific data of notopterol in this work signified the therapeutic effectiveness of notopterol in medicine. Scientific data analysis of the present work signified the biological importance of notopterol in medicine through its therapeutic effectiveness on acute myeloid leukemia, osteoporosis, Alzheimer's disease, pulmonary arterial hypertension and cytochrome P450. Further its antiproliferative, antiseizure, analgesic and pharmacokinetic parameters were also summarized in the present work through scientific data analysis of different scientific research work. Present work signified the biological importance of notopterol in medicine, which will be supportive to all the scientific peoples to explore the medicinal value of notopterol in medicine. However, more scientific investigation is needed in the area of pharmacokinetics and toxicology in order to know its biological significance in human and clinical uses.

Keywords: Antiproliferative, Antiseizure, Analgesic, Acute Myeloid Leukemia, Alzheimer's Disease, Coumarins, Cytochrome P450, Notopterol, Osteoporosis, Pulmonary Arterial Hypertension, Pharmacokinetic

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Traditional and complementary medicines are found in almost every country in the world. Medicinal plants are an important source of raw material for the mass production of many drugs, as well as a source of lead molecules for drug discovery and development. Herbal medicines are playing key role in healthcare system for the treatment of numerous kinds of human disorders such as cancer, hypertension, diabetes, and malaria. The World Health Organization (WHO) has also praised the importance of herbal medicine in the world for the treatment of human disorders.[1–7] In the past decades, public interest of herbal medicines has been increased significantly. The utilization

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of plants as medicine for the treatment of diseases by primitive man has been traced back at least 60 000 years ago. The majority of the natural resources for producing novel lead compounds for therapeutic purposes are derived from plants, animals, fungi, marine species, and microbes. The global demand for medicinal plants may reach an estimate of US$ 7 trillion by 2050.[8–10] The term 'herb' is often utilized freely to allude not just to herbaceous plants yet in addition to bark; roots; leaves; seeds and product of trees, bushes, and woody vines; and concentrates of a similar that are esteemed for their exquisite, fragrant, or therapeutic characteristics.[11] Medicinal plants and their phytochemicals have been used to treat a wide range of diseases since prehistoric times and in modern pharmacotherapy it is recommended to use herbal medicines as an alternative option for the treatment of disease.[12] The use of Traditional Chinese medicine (TCM) has steadily increased every year. In China, TCM accounts for 40% of its pharmaceutical market.[13] TCM is one of the treasures of Chinese culture and has had an irreplaceable part in the prophylaxis and therapy of diseases for thousands of years.[14] Pure active phytochemicals commonly called secondary metabolites derived and developed from various parts of plants have been used as drugs and nutraceuticals. These bioactive phytochemicals have been utilized in healthcare system for different medicinal purpose.[15–19]

Coumarin (2H-1-benzopyran-2-one) is a plant secondary molecule that consists of benzene and 2-pyrone rings. Coumarins belonging to the benzopyrone family can be classified into pyranocoumarins, simple coumarins, furanocoumarins and bis or tris-coumarins on the basis of its chemical diversity. Coumarin and coumarin-related drugs have numerous pharmacological activities, including anticarcinogenic, anti-inflammatory, anticancer, neuroprotective antimicrobial, antioxidant and anti-inflammatory activities. In addition, coumarin-metal complexes have shown a considerable cytotoxic effect on several cancer cells, including K562 cells and A549, HeLa. Inhibition of topoisomerase enzymes, blockage of the cell cycle, and induction of cell apoptosis are the main mechanism of antitumor activity of coumarin.[20–22] Coumarins are naturally found in plants, microorganisms and animals. They have received considerable attention from scientists all over the world because of their anti-microbial, anti-cancer, anti-tuberculosis, anti-HIV, anti-inflammatory, anti-coagulant, anti-proliferative, antioxidant, anti-viral, anti-mutagenic, anti-tumor, vasodilator properties, anti-fungal, and anti-bacterial properties.[23] Coumarin and its derivatives are interesting compounds due to their photochemical, photophysical, and biological properties.[24] Due to their biological activity and sweet-smelling property, coumarin-based molecules have been used as a fragrance enhancer and odor-masking additive. Further, it also have other applications in soft drink, biscuit, and sesame paste, etc.[25] The use of coumarins in biological and medicinal products has received much research. Researchers discovered that coumarin derivatives might be used to create powerful anti-HIV medications.[26] In recent decades, coumarin derivatives have served as chemical probes in laser dyes, fluorescent sensors, organic light-emitting diodes, sensitizers for dye sensitized solar cells, aggregate-induced emission for bioimaging, and medicine.[27] Coumarin heterocyclic structure has been largely studied as it is present in drugs such as warfarin and acenocumarol, which act as vitamin K antagonists. Methoxypsoralen derivatives are popularly used in the treatment of psoriasis and vitiligo. (+)-Calanolide A, a tetracyclic dipyranocoumarin, attracted attention as a potential anti-HIV agent.[28] Coumarin-hemicyanine is a well-known hybrid dye of coumarin and hemicyanine that has become increasingly popular in environmental protection, biochemistry, and disease diagnosis.[29]

Notopterol

Notopterol (Fig. 1) is the major active compound isolated from the Chinese herb *Notopterygium incisum* Ting ex H.T. Notopterol is a furocoumarin class phytochemical and found to have antiinflammatory, anti-apoptotic, analgesic, and anti-oxidant properties. Notopterol significantly induced apoptosis, differentiation and chromatin condensation on human leukemia cell line, HL-60 cells. Furthermore, notop-

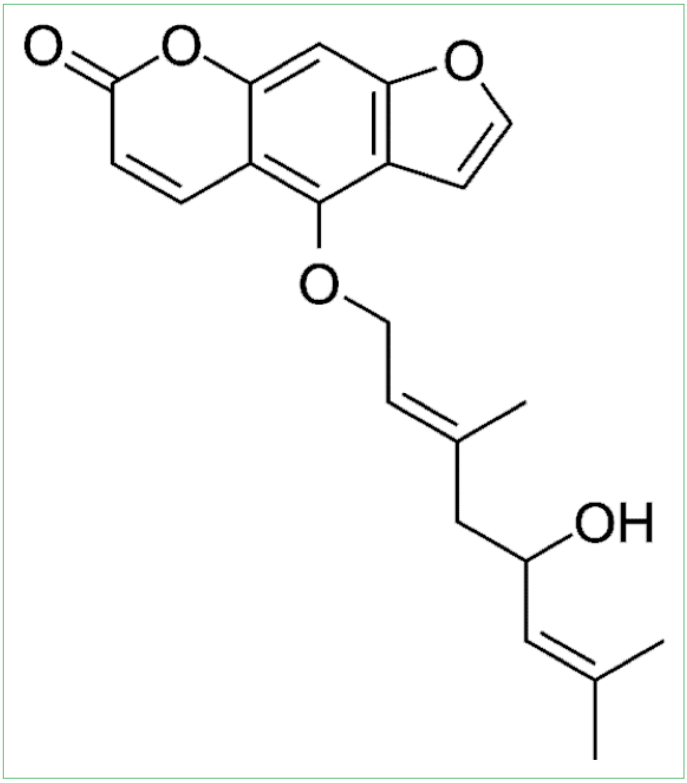

Figure 1. Chemical structure of notopterol.

terol also induced cell differentiation, apoptosis in addition to regulating cell-cycle proteins in human leukemia HL-60 cells. The anti-arthritic effect of notopterol has been studied in CIA model in DBA/1J and C57/BL6mice and resulted in significant reduction in clinical arthritic scores.[30] Notopterol 5[(2E)-5-hydroxy-3,7-dimethyl-2,6-octadienyloxy]psoralen is a linear furanocoumarin extracted from the rhizomes of either *Notopterygium incisum* Ting ex H. T. Chang or N. forbesii Boiss that belong to the Umbelliferae family. Notopterol is one of the main active ingredients of Qianghuo which has been recognized to display analgesic and anti-inflammatory effects.[31] The main active constituents of *Notopterygium forbessi* Boiss (Qianghuo in Chinese) are coumarins, including notopterol.[32] Notopterol, a natural furancoumarin, was identified as a dual-target GSK-3β/BACE1 inhibitor with significant GSK-3β inhibition and moderate BACE1 inhibition capacity.[33] *Notopterygii Rhizoma* et Radix, originating from dried rhizome and root of *Notopterygium incisum* Ting ex H.T. Chang or *Notopterygium franchetii* H. de Boiss, is well known herbal medicine in TCM, which has been officially listed in the Chinese Pharmacopoeia (2015 Edition). Phytochemical investigations of *Notopterygii Rhizoma* et Radix revealed the presence of coumarins notopterol.[34] Notopterol is one of the main constituents of *Notopterygium incisum* Ting ex H.T. Chang and has been reported to have analgesic properties, including the inhibition of acetic acid-induced writhing in mice. Notopterol could directly bind to the three critical sites in the kinase domains of JAK2 (L932/R980/N981) and JAK3 (K830/L905/D967) to inhibit the JAK-STAT signaling, leading to the reduced production of inflammatory cytokines and chemokines.[35] Notopterol, is an active monomer extracted from *Notopterygium incisum* with antipyretic, analgesic and anti-inflammatory effects, which also has been reported to induce cell-cycle-specific inhibition and apoptosis in MCF-7 cancer cell line. Notopterol anti-inflammatory effect is as a result of its inhibitory activity on vascular permeability.[36] Notopterol showed preliminary antiproliferative effects on some cancer cell line, such as HEPG-2, McF-7, and C6, etc. Additionally, it can also inhibit proliferation, apoptosis, differentiation, and cell cycle of human acute leukemia HL-60 cells. Apart from that, notopterol treatment reduced synovitis and structural cartilage and bone damage, reduced the number of F4/80+ and iNOS+ inflammatory macrophages in synovial tissue of mice with collagen-induced arthritis, and inhibited the production of interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and Interleukin 6 (IL-6) proinflammatory factors in the lesion and circulation.[37] Notopterol isolated from *Notopterygium incisum* possesses the analgesic and anticancer activities.[38] Notopterol, the main Secondary metabolite of Notopterygium incisum Ting ex H.T, may have the potential benefits on SARS-CoV2 infection due to its anti-inflammatory, anticancer, and anti-angiogenic properties, and a significant reduction in cytokines and chemokines releasing including TNFa, IL-6, interferon-γ.[39] Traditional herb *Angelicae pubescentis* radix and *Notopterygii rhizoma* et radix also contain notopterol.[40]

Pharmacological Activity of Notopterol

Acute Myeloid Leukemia

Biological effects of notopterol on the apoptosis and differentiation of HL-60 cells has been investigated to explore the underlying molecular mechanisms. Notopterol inhibited the growth of HL-60 cells and reduced the number of colonies. In addtion, notopterol induced the percentage of apoptotic HL-60 cells, reduced the mitochondrial membrane potential, decreased the protein expresstion of Bcl-2 and Mcl-1, and increased the expression of Bax, cleavage of caspase 9, caspase 3, and PARP. Notopterol clearly induced chromatin condensation. Notopterol could induce apoptosis, differentiation, and G0/G1 arrest in human acute myeloid leukemia HL-60 cells, suggesting that notopterol has potential therapeutic effects on acute myeloid leukemia.[41]

Antiproliferative

Bioassay-guided fractionation of the antiproliferative chloroform extract of *Notopterygium incisum* led to the isolation of nine linear furocoumarins. All the isolates were tested against two human cancer cell lines (HepG-2 and MCF-7) and a rat cancer cell line (C6) using the 2,5-diphenyl-2H-tetrazolium bromide (MTT) assay method. Among them notopterol showed significant antiproliferative activity against the HepG-2 and C6 cancer cell lines. Notopterol also showed moderate cytotoxicity against the MCF-7 cancer cell line.[42]

Osteoporosis

Biological potential of notopterol isolated from *Notopterygium incisum* has been investigated for its effectiveness on osteoporosis. Notopterol serves as an inhibitor in regulating receptor activator of nuclear factor kappa B ligand (RANKL)-activated osteoclasts formation and bone resorption function. Furthermore, RANKL-mediated signaling pathways including mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB)and calcium ossification were hampered, whereas ROS scavenging enzymes in Nrf2/Keap1/ARE signaling pathways were promoted by notopterol. Notopterol diminished the loss of bone mass in preclinical model of OVX mice by blocking osteoclastogenesis. Notopterol could arrest osteoclastogenesis and bone resorptive activity by attenuating RANKL-mediated MAPK, NF-κB, calcium and NFATc1 signaling transduction pathways and enhancing ROS scavenging enzymes in Nrf2/Keap1/ARE pathways in vitro, and prohibit bone loss induced by OVX *in vivo*. Notopterol may be identified to be a natural and novel treatment for osteolytic diseases.[38]

Alzheimer's Disease

Notopterol derivatives have been synthesized with furacoumarin as a scaffold in order to enhance their balanced AChE/BACE1/GSK3β inhibitory activity. Fortunately, 1c showed effective inhibitory activity against AChE, BACE1, and GSK3β. Furthermore, 1c showed good blood-brain barrier penetrability, suitable bioavailability, and oral safety. More importantly, 1c could ameliorate the impaired learning and memory in Aβ-induced Alzheimer's disease (AD) mice.[43] Notopterol was docked into the binding site of the proteins. In BACE1, the hydroxyl group of the Notopterol fatty chain interacted with Asp32, Asp228, and Thr231, and formed a water bridge with Gly230. Notopterol can bind to protein in a stable state in the process of molecular dynamics simulation. Inhibitory effect of notopterol on BACE1 and GSK3β enzymes were also tested and found to show moderate inhibitory against BACE1 and strong inhibitory against GSK3β. Inhibition of the activity of BACE1 and GSK3β by notopterol can effectively repair the pathophysiological and cognitive impairment of AD caused by abnormal Aβ accumulation and tau hyperphosphorylation.[44]

Antiseizure

Behavioral antiseizure activity screening of 18 different coumarin derivatives have been investigated in the larval zebrafish pentylenetetrazole (PTZ) model using locomotor measurements. Activity was confirmed for seven compounds, which lowered seizure-like behavior, including notopterol 54%. All of them, except for nodakenetin, showed pronounced antiepileptiform activity, decreasing PTZ-induced elevation in power spectral density (PSD) by notopterol. These data demonstrate the potential of diverse coumarin scaffolds for antiseizure drugs discovery.[28]

Pulmonary Arterial Hypertension

Biological effect of notopterol extracted from the root of *Notopterygium incisum* on monocrotaline (MCT) induced pulmonary arterial hypertension (PAH) rats has been investigated. Notopterol improved mortality rate and RV function while reducing right ventricular systolic pressure in MCT-induced PAH rats. Furthermore, notopterol reduced right ventricular hypertrophy and fibrosis, and it also eased pulmonary vascular remodeling and MCT-induced muscularization. In addition, notopterol attenuated the proinflammatory factor (IL-1β, IL-6) and PCNA in the lungs of PAH rats. Notopterol can inhibit the proliferation and migration of human pulmonary arterial smooth muscle cells (HPASMCs). Notopterol exerts anti-inflammatory and antiproliferative effects in the pulmonary arteries, which may contribute to prevention of PAH.[37]

Analgesic

Notopterol was identified as the analgesic component of *Notopterygium incisum* TING by using the acetic acid-induced writhing method. Notopterol also indicated an anti-inflammatory activity by its inhibitory effect in the vascular permeability test. The intensive prolongation of pentobarbital-induced hypnosis was possibly caused by its inhibitory effect on the drug metabolism in liver.[45]

Cytochrome P450

The inhibitory effects of notopterol on human cytochrome P450 enzymes has been investigated and found that notopterol inhibited the activity of CYP2D6 in a time, concentration and NADPH-dependent manner. After incubation with notopterol at 10 μM for 9 min, approximately 92% of CYP2D6 activity was inhibited.[31] Inhibitory effects of 12 furanocoumarins extracted from plants in the Umbelliferae family against P-gp and CYP3A4 activity has been investigated. From screening of the CYP3A4 inhibitory effect, notopterol was found to be potent inhibitors of CYP3A4.[46] Specific cytochrome P450 3A4 inhibitors which were isolated from grapefruit juice had the same furocoumarin structure as notopterol.[47]

Pharmacokinetic

A specific, sensitive, and reliable high performance liquid chromatography with fluorescence detection (HPLC-FLD) was used for the simultaneous quantification of notopterol in rat plasma using osthole as the internal standard. Separation was carried out with a Hedera™ ODS column (4.6 × 250 mm, 5 μm) by gradient elution. The validated method was successfully used for the simultaneous determination of the four coumarins in *Notopterygium incisum* extracts and also for the pharmacokinetic and excretion study of notopterol in rats.[36]

Analytical Aspects

A specific, sensitive, and reliable high performance liquid chromatography-tandem mass spectrometry method has been developed for the quantitative determination of notopterol enantiomers in *Notopterygii Rhizoma* et Radix. Solid-phase extraction was used for the extraction. The average recoveries of (-)-notopterol and (+)-notopterol were demonstrated to be 99.3 % and 101.1 %, respectively. Finally, the validated method was successfully applied to the quantification of notopterol enantiomers in *Notopterygii Rhizoma* et Radix from different sources.[34] Preparative high-speed counter-current chromatography was successfully used for isolation and purification of coumarins from *Notopterygium forbessi* Boiss (Qianghuo in Chinese). Four major components, including notopterol were isolated with 98% purity.[32] Biological effect of carbohydrate, endogenous hormones and secondary metabolites on the growth and development process of rhizomes of *Notopterygium incisum* has been in-

vestigated. The content of notopterol in rhizomes was found to be higher than that in roots.[48] The content of notopterol increased by 37.96% in *Vicia faba* treatment, respectively, indicating that the intercropping with *Vicia faba* boosted the accumulation of secondary metabolites in *Notopterygium incisum*.[49] Habitat altitude, average air temperature, and vegetation types were the dominant factors contributing to the growth of *Notopterygium incisum*, which also affect the notopterol accumulation in its underground parts.[50] Chemical constituents of different commercial parts as well as fibrous roots of *Notopterygium incisum* has been investigated by high performance liquid chromatography coupled with diode array detection and mass spectrometry (HPLC-DAD-MS). The content of notopterol in fibrous roots was found to be higher than any other parts of *Notopterygium incisum*.[51] Fragmentation patterns of simple coumarins furanocourmarin, furanocourmarin and dihydrofuran coumarin have been studied by mass spectrometry, with reference to notopterol using ultrahigh performance liquid chromatography combined with quardrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS).[52] An improved quality assessment method for Rhizoma et Radix Notopterygii has been developed using fingerprinting and quantitation of marker compounds notopterol using a validated reverse-phase high performance liquid chromatography (HPLC) method.[53] The phenolic constituents and coumarins of Chemical constituents of *Notopterygium incisum* Ting ex H.T. Chang and *Notopterygium forbesii* Boiss were analyzed by high-performance liquid chromatography-photodiode array detection-electrospray ionization tandem mass spectrometry (HPLC/DAD/ESI-MS(n)). A total of 25 compounds were detected in the methanol extracts, including notopterol were the predominant constituents of *Notopterygium incisum*.[54] Nine compounds, including notopterol were isolated from the under-ground part of *Notopterygium forbesii* on the basis of physicochemical properties and spectroscopic analysis.[55] A rapid, sensitive, environmental friendly dual preconcentration method by combining micro matrix solid-phase dispersion extraction with field-enhanced sample injection and micelle to cyclodextrin stacking has been developed for the determination of furocoumarins, including notopterol.[56] Analysis of the underground part of *Notopterygium forbesii* contents by HPLC revealed the presence of notopterol (0.08%), while that of *Notopterygium incisum* contained a large amount of notopterol (1.2%).[57] Effects of different softening method slice thickness and drying methods on the quality of *Notopterygii Rhizoma* et Radix slices, has been investigated and the experimental data were analyzed using notopterol.[58] Adaptive mechanism of *Notopterygium incisum* to water changes has been investigated on one-year-old seedlings used as test materials. At the 70% field capacity, the notopterol were higher than100 field capacity and 40 field capacity.[59] Simultaneous analysis of six biomarkers including notopterol in *Ostericum koreanum* and *Notopterygium incisum* has been developed using HPLC method.[60] An ultra-high-performance liquid chromatography-quadrupole/time of flight mass spectrometry has been utilized to identify 33 compounds in *Notopterygii rhizoma* and radix.[61] Notopterol was the major components for determination of chemical quality of *Notopterygii Rhizoma* et Radix.[62] A method of ultra high performance liquid chromatography with tandem mass spectrometry was developed for the simultaneous quantification of 33 active components including 26 coumarins and 7 phenolic acid esters in *Notopterygii Rhizoma* et Radix and the variations of notopterol, was suggested as important indicators of its quality.[63] The chemical constituents of *Notopterygium incisum* were isolated by column chromatographic methods and structurally elucidated by Nuclear magnetic resonance (NMR) and mass spectra (MS) evidences. Twenty-four compounds were obtained and identified, including notopterol.[64]

Conclusion

The aim of the present work is to collect all the scientific information of notopterol from different scientific databases and analyzed in the present work in order to know the health beneficial aspects of notopterol in medicine. Scientific data of notopterol has been collected in the present work for its biological potential and pharmacological activities with its analytical aspects. However, detailed pharmacological activities of notopterol have also been discussed in the present paper. Moreover, scientific data for analytical aspects of notopterol have been collected and analyzed in the present work through available scientific data of notopterol in different scientific research works. All the scientific data of notopterol have been collected from PubMed, Science Direct, Scopus, and Google in the present work. Presented scientific data signified the therapeutic effectiveness and biological role of notopterol in medicine. Scientific data analysis of the present work signified the biological importance of notopterol in medicine through its therapeutic effectiveness on acute myeloid leukemia, osteoporosis, alzheimer's disease, pulmonary arterial hypertension and cytochrome P450 (Fig. 2). Further its antiproliferative, antiseizure, anal-

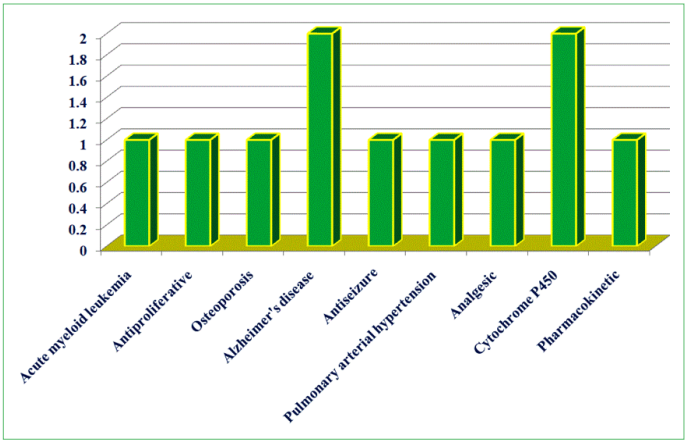

Figure 2. Pharmacological activities of notopterol.

gesic and pharmacokinetic parameters were also summarized in the present work through scientific data analysis of different scientific research work. Present work signified the biological importance if of notopterol in medicine which will be supportive to all the scientific peoples to explore the medicinal value of notopterol in medicine. However detailed preclinical and clinical scientific data is needed in order to claim the therapeutic potential of notopterol on various forms of human disorders. Presented scientific data's of notopterol in the present work will be helpful to the scientific person of all the biological sciences in order to explore the health beneficial aspects of notopterol.

Disclosures

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