Commentary Article

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Plausible Pharmacodynamics Supporting the Bronchodilator

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Description

Diarrhea is one of the leading causes of worldwide disease encumbrance, regardless of significant advancement in public health consciousness and sanitization. Globally, there were more than 4.4 billion cases of diarrhea in 2016, which resulted in 1.6 million fatalities and had a substantial economic and social impact. In accordance with the World Health Organization, diarrhea is characterized by three or more loose or watery stools per day or a rise in the usual number of evacuations. More than 150000 fatalities in Pakistan are attributed to frequent and severe diarrheal episodes, which also cause neonatal malnutrition and developmental retardation. Cough is one of the most prevalent symptoms for which individuals seek primary care globally and the most common complaint of patients seeking treatment at respiratory or allergy specialty clinics. Infection with respiratory viruses such as severe acute respiratory syndrome coronavirus 2 and rhinovirus is a common cause of acute cough and is often self-limiting; however, post-infectious cough can continue for months in particular individuals.

Chronic Cough

Clinical standards describe a chronic cough as one that persists for more than eight weeks in adults and more than four weeks in children; however, in much epidemiological research, a chronic cough is defined as one that persists for more than three months. Chronic cough affects 10% of the population across all demographics. In Pakistan, asthma and chest problems have considerably escalated over the past several decades due to lifestyle changes and growing urbanization. This trend is predicted to continue over the next ten years. WHO estimates that in many underdeveloped nations with inadequate access to modern medications, up to 80% of the population relies on traditional medicines, usually plant-based pharmaceuticals, for primary health care. Such drugs are the main source of health care for the impoverished, and many people utilize them. Therefore, Ethnobotany studies how natives use therapeutic herbs. Man's use of plants as medicinal agents extends to antiquity and is currently a key source of medicine used to treat minor maladies worldwide. Documenting ethnobotanical practices is crucial for preserving this knowledge for future generations and disseminating the information throughout the scientific community, which is helpful for drug discovery and development. Berberis lycium Royle is a member of the Berberidaceae family and is highly esteemed in traditional remedies worldwide. Common names for B. lycium include “Kashmal,” “Kasmal,” and “Ishkeen” in Urdu. B. lycium is a precious medicinal plant with a long history of treating diarrhea and abdominal spasms. Traditionally, it is also used to treat coughs and chest problems. The plant's extract can treat spleen disorders, throat pain, digestive issues, eye burning, and the mending of broken bones. Its roots were primarily utilized to cure hemorrhagic dysentery by the tribal inhabitants of the Kashmir valley. The fruit of B. lycium is used as a coagulant, a hypoglycemic, an anti-carcinogenic, an anti-inflammatory, and an antipyretic. The indigenous populace uses the whole plant to treat rheumatism, jaundice, sore eyes, fractured bones, and ulcers. Animal models have also shown that fruit extract, stem bark, and root bark have anticancer, antioxidant, and antitumor, anti-urolithic, and wound-healing effects. Despite medicinal plants' growing used and popularity, scientific facts supporting their traditional uses and toxicity assessments remained a significant issue.

Antidiarrheal Effects

Consequently, the main goals of this investigation were to identify bioactive compounds in the hydromethanolic extract of B. lycium and to evaluate its antispasmodic, bronchodilator, and antidiarrheal activities with an exploration of the plausible mechanisms using in silico, *in vitro* and *in vivo* studies. It can be concluded that the antispasmodic, bronchodilator and antidiarrheal effects of Berberis lycium Royle may be attributable to a dual blockade of muscarinic receptors and Ca +2 channels. The presence of alkaloids and flavonoids in B. lycium may explain its antimuscarinic and Ca+2 antagonistic properties. The network pharmacology study demonstrated that BLR bioactive chemicals might interfere with the genes and KEGG pathways associated with diarrhea, coughs, and chest problems. Berberis lycium Royle has substantial evidence to support its historical use as a therapy for various diseases, with incredible therapeutic benefits. Consequently, this study aimed to authenticate Berberis lycium Royle's folklore claims and explore its potential fundamental mechanisms to treat diarrhea, coughs, and chest problems. Berberis lycium Royle, a member of the Berberidaceae family, is a high-value medicinal plant with a

documented history of usage in traditional medicine and has demonstrated significant therapeutic results among local populations throughout the globe. It is used traditionally in many parts of Pakistan to treat diarrhea, abdominal spasms, coughs, and chest problems. To investigate the antispasmodic, bronchodilator, and antidiarrheal effects of B. lycium and its possible underlying mechanisms through in silico, *in vitro* and *in vivo* studies. LC ESI–MS/MS analysis was used to identify bioactive components within the hydromethanolic extract of B. lycium. In silico studies, including network pharmacology and molecular docking, were utilized to investigate the antispasmodic and bronchodilator properties of the extract's bioactive components. *In vitro* pharmacological studies were conducted using isolated rabbit jejunum, trachea, urinary bladder, and rat ileum preparations. *In vivo* antidiarrheal activities were conducted in mice, including castor oil-induced diarrhea, intestinal transit, and castor oil-induced enteropooling. The LC ESI–MS/MS analysis of the hydromethanolic extract of B. lycium identified 38 bioactive compounds. Network pharmacology study demonstrated that the mechanism of BLR for the treatment of diarrhea might involve IL1B, TLR4, PIK3R1, TNF, PTPRC, IL2, PIK3CD, and ABCB1, whereas, for respiratory ailments, it may involve PIK3CG, TRPV1, STAT3, ICAM1, ACE, PTGER2, PTGS2, TNF, MMP9, NOS2, IL2, CCR5, HRH1, and VDR. Molecular docking research revealed that chlorogenic acid, epigallocatechin, isorhamnetin, quinic acid, gallic acid, camptothecin, formononetin-7-O-glucoside, velutin, caffeic acid, and (S)-luteanine exhibited a higher docking score than dicyclomine with validated proteins of smooth muscle contractions such as CACB2_HUMAN, ACM3_HUMAN, MYLK_HUMAN, and PLCG1_HUMAN. *In vitro* investigations demonstrated that Blr.Cr, Blr.EtOAc, and Blr.Aq relaxed spontaneously contracting jejunum preparations; carbachol (1 µM)-induced and K+ (80 mM)-induced jejunum, trachea, and urinary bladder contractions in a concentration-dependent manner, similar to dicyclomine. Moreover, Blr.Cr, Blr.EtOAc, and Blr.Aq exhibited a rightward shift in Ca+2 and carbachol cumulative response curves, similar to dicyclomine, demonstrating the coexistence of antimuscarinic and Ca +2 antagonistic mechanisms due to the presence of alkaloids and flavonoids. *In vivo* antidiarrheal activities showed that the hydromethanolic extract was significantly effective against castor oil-induced diarrhea and castor oil-induced enteropooling, similar to loperamide, and charcoal meal intestinal transit, similar to atropine, in mice at doses of 50, 100, and 200 mg/kg body weight, which supports its traditional use in diarrhea.