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Herbal Treatment: An Alternative Therapy for the Recovery of Gastric Ulcers Caused by Nonsteroidal Anti-Inflammatory Drugs

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Abstract

Chinese herbal medicines (CHMs) have been used successfully to treat infectious disorders, however it is yet unknown how well they work to cure infections caused by XDRE, or extensively drug-resistant enterobacteria. Here, we developed a retrospective multicenter study with 766 patients who had both nonfermentative bacteria (NFB) and XDRE infections to examine the efficacy of CHMs in combination with antibiotics in treating XDRE infections in a cohort of patients and to compare it to standard antibiotic monotherapy. After a 14-day course of treatment, the 547 patients who had agreed to CHMs and antibiotic therapy did so with a higher level of satisfaction than the 219 patients who had received antibiotic monotherapy. White blood cell count (WBC) and neutrophil percentage (N%) were the two main assessment indicators. The secondary evaluation indices included body temperature, breath rate, heart rate, platelets, haemoglobin, red blood cell, albumin, creatinine, glucose, and 28-day survival rates. Briefly stated, in our experience, CHMs combined with antibiotic therapy resulted in more desirable effectiveness in treating XDRE infections than antibiotic monotherapy, and CHMs may be an extremely valuable resource in the field of managing XDRE infections and illuminating the research and development of new antibiotics. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed therapeutic drug classes used globally to treat a wide range of medical conditions, including pain, inflammation, cardiovascular complications, and many other diseases. However, NSAIDs may have adverse effects, including gastroduodenal disorders. Therefore, there is a rising interest in and need for finding safe, antiulcer plant-based formulations to treat gastric ulcers brought on by NSAID use. Numerous natural plants, including Camellia sinensis, Phyllanthus emblica, Myristica malabarica, Piper betle, Picrorhiza kurroa, and others, have been the subject of extensive research. These plants' active constituents have been shown to inhibit NSAID-induced gastric ulcers through their antioxidative and immunomodulatory activity. As a result, using herbal remedies regularly may help to reduce other negative effects such stomach ulcers caused by NSAIDs.

Keywords: Herbal; Nonsteroidal

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Introduction

Since the discovery of penicillin, antibiotics have helped millions of patients worldwide and transformed the study of infectious illnesses. However, because antibiotics, like carbapenem, have been overused, a crisis has arisen where many antibiotics are no longer effective against even the most basic infections globally, and antimicrobial resistance has been regarded as one of the most serious global public health threats of this century. More and more bacterial species are becoming resistant to the widely used antibiotics. Extensively drug-resistant enterobacteria (XDRE)

are a class of nonfermentative Gram-negative bacteria that are naturally or acquiredly drug-resistant to 5 to 7 different types of antibiotics, including Pseudomonas aeruginosa (PsAr) and Acinetobacter. Especially among patients in intensive care units (ICU) and with other critical conditions, infections brought on by such bacteria frequently lead to an increase in hospitalisation, an increase in treatment failures, a rise in morbidity and death, and a lengthening of hospitalisation **[1]**. According to a conservative estimate from the US Center for Disease Control and Prevention (CDC), more than two million Americans suffer from antibiotic-resistant diseases each year, with at least 23,000 of them passing away as a result. In 2007, it was projected that the most prevalent multidrug-resistant bacteria in Europe were responsible for 400,000 illnesses and 25,000 fatalities **[2]**. This means that these germs not only pose a substantial risk to public health on a worldwide scale, but they also place a heavy load on healthcare systems. Tropical plants can be found in countless types in India. Kabiraji medicine, which makes use of these healing plants, has a long history among Native Americans. Ayurvedic medicine is acknowledged by the 1970 Indian Medicine Central Council Act **[3]**. Research on Ayurvedic therapies is also supported and encouraged by the World Health Organization. About 5000 years ago in China, herbal medicine was first used. Because of their antioxidant properties, plant extracts from a variety of species have been employed as medicinal treatments for a wide range of ailments. Spices and herbs are well-known sources of phenols and aromatic amines, which are natural antioxidants in large quantities. These can exert their effects on a variety of levels by lowering local oxygen concentrations, reducing superoxide formation, inhibiting chain initiation, metal-induced free radical generation, and lipid peroxidation **[4]**. Numerous medicinal plants have been shown in clinical studies to be effective in treating gastrointestinal diseases, and basic scientific study has identified many of the mechanisms behind these therapeutic actions. A common condition known as a gastric ulcer causes bleeding from perforations in the gastrointestinal mucosa. The total prevalence rate of the condition ranged from 1 to 6.5 per thousand in the age category of 15 years and above in a chosen urban population, according to a report by the Indian Council of Medical Research on the epidemiology of stomach ulcer in India. Mahadeva and Goh have analysed and reported on the epidemiology of this illness in great detail. There are a number of causes for this gastric ulcer condition, but 70% to 80% of them are related to Helicobacter pylori infection, a spiral-shaped, gram-negative bacteria **[5]**. However, with an increasing tendency, about 25% of instances of stomach ulcers are caused by the use of nonsteroidal anti-inflammatory medicines. NSAIDs are among the medications that are most frequently given worldwide and are frequently used to treat clinical conditions, including pain and inflammation. These medications are known to cause stomach ulceration and slow the healing of ulcers, though. Despite recent developments, a suitable treatment for NSAID-induced gastropathy is still difficult to find. The need for developing medications with plant origins has been emphasised by the World Health Organization **[6]**.

Patients and Methods [7]

The pulmonary, urinary, or surgical wound systems could all be contaminated. Additionally, combined infection with two or three different bacteria was seen. Patients would be disqualified if they had any mental problems, had participated in any other clinical trials, were pregnant or nursing, had an allergy to any CHMs, or if their complete medical records could not be obtained. Prior to enrolment, each patient signed a written informed consent form. This survey consisted a total of 766 cases, who were divided into treatment groups using traditional Chinese medicine (TCM) and antibiotics (the Control group) based on the therapeutic intervention **[8]**. The 219 patients in the Control group chose to receive antibiotic monotherapy instead of the TCM herbal mix that was used to treat the 547 patients in the TCM group. Doctors made all of the treatment decisions because the infections were all brought on by highly drug-resistant bacteria, and some patients were even afflicted with many types of bacteria. Carbapenems, cephalosporin, and aminoglycosides were the antibiotics utilised in this study; there were no restrictions on medication combinations. The antibiotic dosage was chosen based on the dispensatory and creatinine clearance rates. The 547 TCM patients agreed to receive both Chinese medicine and antibiotic medication. Decoction, Chinese-patent medications, and Chinese medicine parenteral solutions were all forms of applied Chinese medicine. The treatment's main goals were to eliminate heat, detoxify, strengthen Qi, and activate circulation. Flos Lonicerae, Radix Angelicae Sinensis, Radix Astragali seu Hedysari, and other herbal remedies were often utilised (Huang qi). Additionally, some prescriptions included Fructus Gardeniae, Radix Paeoniae Rubra, and Radix Rehmanniae Recens **[9]**. This study comprised a total of 766 cases, who were divided into two treatment groups based on the therapeutic approach: antibiotics and traditional Chinese medicine. The 219 patients in the Control group chose antibiotic monotherapy whereas the 547 patients in the TCM group received treatment with a TCM herbal combination mixed with antibiotics. Since all of the infections were brought on by bacteria that were highly drug resistant and some patients were even afflicted with multiple pathogens, doctors made all of the final decisions regarding the course of therapy.

Gastric Ulcer

The analgesic and antipyretic medications known as nonsteroidal anti-inflammatory medicines (NSAIDs) are well-known. Aspirin, Indomethacin, Ibuprofen, Naproxen, and similar NSAIDs are frequently prescribed to treat pain, inflammation, colon cancer, cancer, cardiovascular disease, rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, and many other conditions. Several of the most popular anti-inflammatory medications and how they work. The use of these painkillers over an extended period of time, however, poses a serious gastroduodenal risk. 25% of people who have gastric ulcers as a whole have one that was brought on by using NSAIDs, and this number is rising daily. Epithelial, intraepithelial, and subepithelial levels of the gastroduodenal barrier are all affected by NSAIDs. It alters pepsins' ability to perform proteolytic action at the epithelium level by reducing mucus formation and secretion. As a result, the mucus becomes less viscous and less electrically conductive, which encourages ion back diffusion. As ionised NSAIDs remain trapped inside the epithelium, it results in epithelial denudation at the intraepithelial level as a result of direct cellular injury. It causes vasoconstriction of the arterioles

and subepithelial thrombosis in the microcirculation. Oxidative injury and gastrointestinal lesions were caused by NSAIDs. The term "oxidative stress" describes a scenario in which the production of reactive oxygen/reactive nitrogen species (ROS/RNS) and antioxidant defence are seriously out of balance. This is brought on by decreased antioxidant levels, mutations in the antioxidant defence enzymes, or an increase in ROS/RNS production, and it is brought on by a variety of endogenous and exogenous sources. This causes significant damage to important biomacromolecules, which in turn causes a number of disorders, including stomach ulcers. It is now widely accepted that neutrophil infiltration, ROS production, cytokine dysregulation, and the start of lipid peroxidation all play important roles in the pathophysiology of peptic ulcer.

Nitrogen Metabolizing Enzymes [10]

Although nitric oxide (NO) is one of the primary mediators of gastrointestinal mucosal defence, depending on the concentration of NO, it can also cause mucosal injury. It has been observed that the constitutive NOS isoform of endothelial nitric oxide synthase only produces small quantities of NO. In contrast, the inducible version of NOS (iNOS) generates greater amounts of NO. Wallace and Miller demonstrated that NO mediates a critical role in modulating several components of mucosal defence, including increased gastric blood flow, decreased neutrophil adhesion, and increased mucus secretion **[11]**. It was shown that indomethacin-induced gastric ulceration gives a 12-fold increase in gastric epithelial expression of iNOS activity compared with controls, which is correlated with the damage of epithelium.

Therapy of Gastric Ulcer [12]

Depending on the patient's age, general health, medical history, the severity of the aetiology, tolerance for medications, surgeries, or therapies, expectations or preferences, the doctor will choose a specific course of therapy for stomach and duodenal ulcers. In addition, a number of individual factors, including stress, pepsin and acid secretion, alcohol, caffeine, and smoking, are thought to contribute to the onset of stomach or duodenal ulcers. Therefore, the most basic form of treatment, which frequently involves lifestyle modifications like giving up alcohol, smoking, and stress, is abstinence. Initially, the primary treatment strategy aimed to lessen the production of stomach acids, which were thought to be the only factor in the development of ulcers. In the present, the mucosal defence is being strengthened while acid secretion is being decreased as the therapy strategy. Single or combinations of medications are frequently used to treat peptic ulcers. The medical support is created either singly or in combination by blocking the receptor sites, such as with an H2 receptor antagonist, inhibition of intracellular mechanism involving calcium and/or c-AMP, protection of gastric mucosa (cytoprotective function) from chemically induced injury, H+K+-ATPase, inhibition of terminal step of acid secretion, and eradication of H. pylori infection. Currently, the only treatment option for extremely severe illnesses is regular open surgery **[13]**. Although the rates of morbidity have dropped, these medications have a number of negative side effects, such as relapses of the disease, and are sometimes expensive for the underprivileged. It has been established by numerous research that not all NSAIDs have the same ability to cause stomach ulcers. Therefore, a mechanistic approach to drug development may result in the development of novel NSAIDs that are both clinically and user-safe. As prospective alternatives to NSAIDs, NO-NSAIDs and H2S-NSAIDs have recently come under investigation. The group of substances known as nitric oxide (NO)-NSAIDS is novel. NSAIDS including aspirin, flurbiprofen, naproxen, diclofenac, ibuprofen, and indomethacin that release NO are linked via an ester to create these drugs. NO-NSAID does not harm the gastrointestinal mucosa, and it does not prevent the healing of existing ulcers.

Antiulcer Herbal Medicines [14]

The potential for safe and potent antiulcer medications in herbal and other indigenous sources has not been sufficiently investigated. Despite the fact that several plants and their isolated components have been claimed to have significant antiulcer potential over the past three decades, the studies have not been carried out to a logical conclusion to determine their clinical usefulness, unlike with many contemporary drugs like H2 receptor antagonists and proton pump inhibitors. It belongs to the genus of plants known as Apiaceae and is frequently called celery. Also used to treat rat stomach ulcers is a celery ethanol extract **[15]**. It has been demonstrated that ethanolic celery extract has antigastric ulcer efficacy against indomethacin, cytodestructive drugs, and cold restraint stress caused ulceration in rats. The doses were 250 and 500 mg/kg body weight. Due to its antioxidant activity, apium graveolens extract significantly safeguards the gastric mucosa and reduces the baseline gastric output in rats. Bilberry reduced the frequency and severity of ulcers that were inflicted on animals during experiments.

Discussion

Sepsis, which can lead to secondary organ malfunction and bone marrow depression, can be brought on by a severe infection. Thus, it is crucial for the therapy process that internal organ function is monitored. The Cr level is a marker of kidney function, whereas the TBIL and ALB markers of liver function, the HGB, RBC, and PLT markers of bone marrow depression, and the GLU marker of metabolic condition and stress response to some extent. Therefore, as a secondary evaluation of the effectiveness, we also incorporated these indexes. The findings revealed that, compared to the Control group, the TCM group's Cr and GLU reduced, while HGB and ALB grew more considerably. Additionally, the PLT curve was maintained more steadily in the TCM group than in the Control group, and these manifestations pointed to a better outcome. A therapeutic challenge often results from XDRE infection. Resistance mechanism abnormalities play crucial roles in the development of XDRE infection, in addition to the direct harm caused by the pathogenic bacteria and the toxins. Antibiotic monotherapy may suppress the reproduction of T and B cells at the extremely early stage following infection, so impacting the immunologic function, even though there are still few antibiotics available. This is one reason why the effectiveness and safety are not desirable and stable. Since ancient times, CHMs have been successfully employed to treat a variety of infectious disorders; both experimentally and therapeutically, antibacterial properties

have been found in various CHMs or formulas. CHMs may be more successful at treating XDRE infection than conventional antibiotics because of their multicomponents and multitargets properties. Nonsteroidal anti-inflammatory drug (NSAID) use is a common cause of stomach ulcers in addition to other known risk factors. NSAID is a general term that refers to many medications with different chemical make-ups. The digestive system is a complex organ in terms of its function. The normal physiology of the stomach may be affected by drug-induced functional modifications, which may result in gastric lesions and the development of an ulcer. Among the illnesses that cause morbidity and mortality, NSAID-induced stomach ulcers comes in at number four. Despite recent developments, a cure for NSAID-induced gastropathy has so far eluded researchers and clinical practitioners alike, raising concerns. NSAID-induced stomach ulcers are currently treated with a variety of medications, including H2 receptor antagonists, proton pump inhibitors, and antacids. However, their prolonged usage has serious adverse effects, and the less affluent rural populace cannot afford them. The Ayurvedic school of medicine is the oldest in this region of the globe, and India is one of the countries with the greatest wealth in medicinal plants. In order to create effective antiulcer medications that are primarily free of these ingredients, a search among medicinal plants is still crucial.

The drawbacks of a retrospective study lacking a systematic, standardised follow-up and the unavoidable loss to follow-up are some of the remaining limitations of our investigation. Further investigation of the putative mechanism involving CHMs in treating XDRE infections is still required because the study did not document any side outcomes. The treatment plan also varied depending on the case. Each prescription was chosen by the doctor, whether it be for an antibiotics therapy or a CHM therapy. So, the efficacy evaluation can only be subjected to a simple analysis. Due to these problems, the study's credibility suffered. The preliminary evidence this study offers on the success of CHMs in treating XDRE infection, however, makes it still significant.

Conclusion

The ability of plants to produce aromatic compounds like phenols and flavonoids, which act as a defensive mechanism against various ailments, is what gives them their therapeutic potential. These chemicals boost cellular defence activity and scavenge free radicals produced after NSAID use. In comparison to antibiotic monotherapy, CHMs paired with antibiotic therapy treated XDRE infections more successfully, suggesting that CHMs could be a significant resource for XDRE infection management and provide insight for the development of novel medicines.

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Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

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