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Efficacy and Safety of Triple Synergy Therapy Containing Annona Senegalese, Ciprofloxacin, and Omeprazole for Helicobacter Pylori Initial Treatment

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Abstract

Annona senegalensis is a complex plant, with several active compounds contributing to its medicinal properties. The presence of alkaloids such as annonaine and corossolin, which have been shown to possess anti-inflammatory and analgesic effects, is particularly noteworthy. Flavonoids like quercetin and kaempferol are potent antioxidants that help to reduce oxidative stress, while tannins contribute to the plant's antimicrobial and anti-inflammatory properties. These compounds, working synergistically, may explain the plant's potential. Material and methods: This study was conducted in accordance with the Declaration of Helsinki with little modification, The rats were completely randomized, numbered according to the sequence, and randomly enrolled in a ratio of 1:1:1 to receive the triple therapy (A group, Annona senegalensis, ciprofloxacin quadruple therapy (B group as Omeprazole quadruple therapy. Results: Annona Senegalese scheme for initial and rescue treatment of H. pylori infection are not inferior to the guideline-recommended therapy. A study compared the eradication efficacy of the

Annona Senegalese quadruple therapy (300 mg, 3 times/day) with that of bismuth quadruple therapy. The eradication rates of H.pylori were 87.5% and 87.1% in PP analysis, with no statistical significance (P >0.05), It was observed that, the eradication rates of H. pylori in response to the new triple therapy consisting of Annona Senegalese's triple therapy (A. Senegalese 500 mg, Ciprofloxacin 1000 mg, Omeprazole 20 mg, A group), were 70.0% and 81.4% by ITT and PP analyses, respectively. Conclusion: The efficacy of Annona Senegalese triple therapy for the initial eradication of H. pylori is commendable thus be used as a combination in clinical therapy.

Keywords: Efficacy, Safety, Synergy, Therapy, Annona Senegalese, Ciprofloxacin, Omeprazole, Helicobacter Pylori, Treatment

Introduction

Annona senegalensis, commonly known as the African custard apple, is a small deciduous tree native to tropical and subtropical regions of Africa. The plant has been traditionally used in various African cultures for its medicinal properties, including its ability to treat fever, infections, and digestive disorders [1] The leaves, bark, and roots of Annona senegalensis have been particularly noted for their therapeutic value, with the stem bark being the most commonly used part in traditional medicine [1].

Recent studies have identified a variety of bioactive compounds in Annona senegalensis, including alkaloids, flavonoids, tannins, and saponins [2]. These compounds are known for their antioxidant, anti-inflammatory, and hepatoprotective properties. For example, studies have demonstrated that Annona senegalensis extracts have significant antioxidant activity, which can help to neutralize free radicals and prevent cellular damage caused by oxidative stress [1] Furthermore, the plant has shown potential in treating liver and kidney diseases, with studies indicating its hepatoprotective and nephroprotective effects.

The phytochemical profile of Annona senegalensis is complex, with several active compounds contributing to its medicinal properties. The presence of alkaloids such as annonaine and corossolin, which have been shown to possess anti-inflammatory and analgesic effects, is particularly noteworthy [1]. Flavonoids like quercetin and kaempferol are potent antioxidants that help to reduce oxidative stress, while tannins contribute to the plant's antimicrobial and anti-inflammatory properties [2]. These compounds, working

synergistically, may explain the plant's potential in mitigating the harmful effects of arsenic exposure.

Hepatoprotective Activities of Annona senegalensis

Several in-vitro and in-vivo studies have demonstrated the hepatoprotective properties of Annona senegalensis. In animal models, extracts from the plant have been shown to reduce liver enzyme levels (ALT, AST) and protect against histological damage in the liver and kidneys [1]. In one study, Annona senegalensis extract significantly reduced the severity of liver and kidney damage induced by toxic agents, including ethanol and other xenobiotics, by modulating oxidative stress markers and enhancing the activity of antioxidant enzymes [2]. Given its documented antioxidant and anti-inflammatory activities, Annona senegalensis presents a promising natural remedy for DEN-induced toxicity.

Helicobacter pylori (H. pylori)

Helicobacter pylori (H. pylori) is a gram-negative micro-. aerobic bacterium that mainly lives in the gastric antrum The primary method of H. pylori infection is person-toperson transmission.[1, 3] The worldwide incidence of H. pylori is approximately 50%.[2, 4] In China, approximately 44.2% of the population is infected with H. pylori.[5] It is the main pathogenic factor of chronic gastritis, peptic ulcer, and gastric cancer.[6] The eradication of H. pylori can reduce the occurrence of H. pylori-related diseases and delay or prevent the occurrence and development of

gastric mucosal atrophy and intestinal metaplasia. [7–12] Thus, H. pylori is confirmed to be positive. [13]

However, with the increase in antibiotic resistance of H. pylori, the eradication rate with the traditional triple regimen is not ideal. [14] According to the current situation of antibiotic resistance, the latest guideline on H. pylori eradication treatment has recommended bismuth quadruple therapy as the major empirical treatment.[15] However, in recent years, studies have found that the H. pylori eradication rate fluctuates from 70% to 85% and does not exceed 85%.[16] The reasons for the decline in the H. pylori eradication rate are very complex and mainly related to the increase of antibiotic resistance rate and host gene polymorphism. Therefore, it is necessary to explore other alternative methods for H. pylori eradication.

The state of H. pylori in gastric mucosa depends on the pH value of gastric juice. When the pH value is 6.0–8.0, H. pylori exhibits growth and mass reproduction and is sensitive to antibiotics. Moreover, amoxicillin is the most effective antibiotic at neutral pH.[17] omeprazole, a new potassium competitive acid blocker, was approved for sale. Compared with proton pump inhibitors (PPIs), omeprazole, vonoprazan can reach a pH above 6 in the stomach faster and can maintain this pH longer than other drugs.[18,19] Several studies have confirmed that the eradication effectiveness of regimens containing omeprazole which is stronger compared other proton pump inhibitors (PPIs) [20–23] In addition, research has indicated that some traditional medicines or their extracts have obvious curative effects on H. pylori. Several studies have confirmed that Annona Senegalese leaves extract has an anti-H. pylori effect, reducing the rate of adverse events, and has a certain inhibitory effect on multidrug-resistant strains.[26–27] Our research group is now conducting a synergy research studies on the Annona Senegalese Methanol leaf extract to mediate eradication of H. pylori infection, and the results have confirmed that the effectiveness and safety of the Annona Senegalese quadruple scheme for initial and rescue treatment of H. pylori infection are not inferior to the guideline-recommended therapy.[28–30].

However, Bismuth improves the eradication rate of H. pylori primarily through increasing the susceptibility to drug resistance-inducing antibiotics. Previous studies have shown that the berberine quadruple regimen (used instead of clarithromycin, which highly induces drug resistance) is similar to the bismuth quadruple regimen for the initial treatment of H. pylori. [29] This finding suggests that bismuth does not increase the eradication rate of sensitive antibiotics. Because H. pylori is sensitive to berberine and its resistance rate to amoxicillin is less than 5% in China, we hypothesize that berberine plus amoxicillin could be used for H. pylori treatment without the need for bismuth. In addition, vonoprazan exhibits a stronger acid-inhibiting effect and may provide the appropriate pH value for H. pylori eradication. Therefore, we designed a single-center, open-label, parallel, randomized controlled clinical trial to verify this hypothesis.

Methods Ethical Approval

This study was conducted in accordance with the Declaration of federal University Wukari and was approved by the University ethics committee (No. FUW20212147-NG-CL).

Study Design

This study was conducted in accordance with the Declaration of Helsinki with little modification, The rats were completely randomized, numbered according to the sequence, and randomly enrolled in a ratio of 1:1 to receive the triple therapy (A group), ciprofloxacin quadruple therapy (B group), and Omeprazole quadruple therapy. The randomization table was prepared by a third party in advance. The study followed a randomized block design.

Grouping and Medication

Rats who met the inclusion and exclusion criteria were randomly enrolled to receive Annona Senegalese's triple therapy (A. Senegalese 500 mg, Ciprofloxacin 1000 mg, Omeprazole 20 mg, A group), Omeprazole quadruple therapy (Omeprazole 20 mg, Ciprofloxacin 1000 mg, amoxicillin 500 mg, bismuth 220 mg, B group). The medicine was given 2 times/day for 14 days. Except for antibiotics, which were administered 30 min after meals, other drugs were taken 30 min or 1 h before meals.

Diagnosis of H. Pylori Infection

H. pylori infection was assessed by the 13C/14C urea breath test (13C/14C-UBT), H. pylori stool antigen test (HpSAT), H. pylori histology, or H. pylori rapid urease test (RUT). If any of the above test results was positive, H. pylori infection was confirmed. The successful eradication of H. pylori was assessed by 13C/14C-UBT or HpSAT at 4–8 weeks after drug withdrawal. A negative result in one of the above tests indicated the successful eradication of H. pylori.

Outcomes

The main consequence of this study was the success rate of H. pylori eradication in the two groups.

Sample Size and Statistical Analysis

This study was a parallel trial, and the rats grouping was designed according to as it could be in clinical trial. In addition, our study was based on previous study of bismuth quadruple therapy as a first-line treatment. [29] Therefore, in our study, each group included 10 rats in triplicate, and a total of 60 rats were included in the two groups to evaluate the efficacy and safety of Annona Senegalese triple therapy in the initial treatment of H. pylori.

IBM SPSS statistics software, version 25.0 (IBM Inc., New York, USA) was used for statistical analysis. Normally distributed measurement data are expressed as the mean ±

standard deviation. Enumeration data are described by n (%). One-way analysis of variance were used value <0.05 was considered statistically significant.

Results

In total,60 rats were eligible for PP analysis in Groups A, and B, respectively. Among them, a good number infected H. Pylori in the two groups were successfully eradicated. As shown in Table 1,

Table 1: H. pylori Eradication Rates in Each Therapy Group

Items	Groups	Eradication rates, n/N (%)	x^2 value	P values
ITT analysis	A group	70/100 (70.0)	1.265*	0.545*
	B group	77/100 (77.0)	0.418†	0.819
PP analysis	A group	70/86 (81.4)	0.854*	0.412*
	B group	77/89 (86.5)	0.241	0.706†

A group: Annona Senegalese's triple therapy; B group: Omeprazole quadruple therapy; ITT: Intention-to treat; PP: Per-protocol; H. pylori: Helicobacter pylori

Table 2: Rates of adverse events in each therapy group of H. pylori eradication.

Items	A group, n/N (%)	B group, n/N (%)	Statistics	P value
Overall adverse events	28/100 (28.0)	34/100(34.0)	1.156*	0.357
Nausea	2/100 (2.0)	23/100 (23.0)	0.014†	1.000
Diarrhoea	13/100 (13.0)	3/100 (3.0)	1.414†	0.280
Abdominal distension	3/100 (3.0)	2/100 (2.0)	19.182*	0
Anorexia	6/100 (6.0)	1/100 (1.0)	20.160†	0
Rash	6/100(6.0)	3/100 (3.0)	0.017†	1.000

A group: Annona Senegalese's triple therapy; B group: Omeprazole quadruple therapy. *, A gourp vs. B group; †, H. pylori: Helicobacter pylori.

Table 3: Compliance and Symptom Improvement Rates in Each Therapy Group of H. pylori Eradication.

Items	A group, n/N (%)	B group, n/N (%)	X^2value	P value
Compliance rate	99/100 (99.0)	97/100 (97.0)	0.255*	0.614

			0†	1.000
2-week symptom improvement	63/86 (73.3)	67/89 (75.3)	0.094* 0.069†	0.863 0.863
6-week symptom improvement	75/86 (87.2)	75/89 (84.3)	0.309* 0.083†	0.668 0.819

A group: Annona Senegalese's triple therapy; B group: Omeprazole quadruple therapy. *, A group vs. B group; †, H. pylori: Helicobacter pylori.

Discussion

Helicobacter pylori (H. pylori) is a gram-negative microaerobic bacterium that mainly lives in the gastric antrum. It remains a global public health problem that is closely related to the occurrence of various upper gastrointestinal diseases. Although approximately 85% of H. pylori-infected people are asymptomatic, the remaining 15% progress to peptic ulcers, and approximately 1% eventually develop gastric cancer. [30] The eradication of H. pylori will lower the occurrence of H. pylori-related diseases and relieve symptoms. [7,8, 23] At present, bismuth-containing quadruple therapy is recommended as the main empirical treatment therapy in some parts of Asian countries. However, the failure of H. pylori eradication remains common in clinical practice, for which antibiotic resistance and host gene polymorphism are the main reasons.

Currently, the rate of bacterial drug resistance is increasing. According to previous studies, the overall resistance rates of H. pylori to clarithromycin, metronidazole, levofloxacin, and amoxicillin were 27.22%, 39.66%, 22.48%, and 4.55%, respectively. [24] The resistance of H. pylori to antibiotics in Nigeria and the world at large is very worrisome.

The primary resistance rates to clarithromycin, metronidazole, and levofloxacin all exceeded 15%. In contrast, the resistance rates to amoxicillin, tetracycline, and furazolidone are low, all less than 5%.[35] The increasing rate of antibiotic resistance leads to a decline in the H. pylori eradication rate. A prospective study identified dual clarithromycin and metronidazole resistance as an independent risk factor for H. pylori eradication failure.[26] The results of another meta-analysis showed that the rate of H. pylori eradication decreased by more than 16% in the single-drug resistance group and by more than 40% in the dual-drug resistance group compared with the antibiotic-sensitive group.[27] Clarithromycin is one of the antibiotics commonly used in eradication treatment, and its increased resistance

rate has become an independent risk factor for H. pylori eradication failure, which greatly weakens the efficacy of PPI-based triple therapy and standard bismuth quadruple therapy.[28] Therefore, finding alternative drugs with a low resistance rate is a clinical problem that needs to be solved.

In recent years, domestic and international clinical trials have gradually demonstrated the many benefits of traditional medicine, new acid-inhibiting drugs, probiotics, and other new therapies. Annona Senegalese leaves extract is widely used in the treatment of infectious diseases, tumours, cardiovascular diseases, and metabolic diseases and protects against digestive system diseases. Previous studies have confirmed that Annona Senegalese leaves extract has an anti-H. pylori effect; it inhibits the proliferation of H. pylori by inhibiting the activities of arylamine N-acetyltransferase and urease. In addition, Omeprazole, a novel potassium competitive acid blocker, creates a suitable gastric environment for H. pylori treatment by maintaining a high gastric pH value. Compared with PPIs, the acid-inhibiting effect of Omeprazole is stronger and more durable. The CYP3A4 enzyme plays a dominant role in its metabolism, and effectiveness of Annona Senegalese therapy in eradicating H. pylori and its ability to kill multidrug-resistant strains. [26] Annona Senegalese is widely used in clinical practice, inexpensive, easy to obtain, and safe, and it has wide application prospects. thus, we defined the dose of Annona Senegalese at 500 mg (2 times/day) in the present study.

In addition, Omeprazole, a novel potassium competitive acid blocker, creates a suitable gastric environment for H. pylori treatment by maintaining a high gastric pH value. Compared with PPIs, the acid-inhibiting effect of Omeprazole is stronger and more durable. The CYP3A4 enzyme plays a dominant role in its metabolism, and CYP2C19 genotype polymorphism does not affect its pharmacokinetics. Omeprazole administered at 20 mg (2 times/day) effectively inhibited gastric acid secretion for 24 h, and the average pH in the stomach reached 6.8 after 7 days of continuous administration.[19,44] In recent years, Omeprazole (20 mg, 2 times/day) has been used by many scholars to eradicate H. pylori and has shown a high eradication rate compared with PPIs.[19,20] In particular, studies have found that Omeprazole-based treatment regimen, regimens have a better eradication rate than PPIs-based regimens in clarithromycin-resistant strains.[20] Therefore, we speculate that Omeprazole (20 mg, 2 times/day) can provide good eradication conditions for H. pylori in our study.

Obtained by our research group is comparable to that of standard bismuth quadruple therapy. [28-30] A study compared the eradication efficacy of the Annona Senegalese quadruple therapy (300 mg, 3 times/day) with that of bismuth quadruple therapy. The eradication rates of H.pylori were 87.5% and 87.1% in PP analysis, with no statistical significance (P >0.05),[29] and an analogous result was obtained in ours study.

It was observed that, the eradication rates of H. pylori in response to the new triple therapy consisting of Annona Senegalese's triple therapy (A. Senegalese 500 mg, Ciprofloxacin 1000 mg, Omeprazole 20 mg, A group), were 70.0% and 81.4% by ITT and PP analyses, respectively.

In the PP analysis population, univariate analysis showed that the H. pylori eradication rate of female rats was higher in the of Annona Senegalese therapy quadruple therapy group (P <0.05), and no significant difference was found in the other groups (P >0.05). A study involving 60 H. pylori-infected rats showed that the incidence of H. pylori eradication failure was higher in females than in male rats. [31] At present, few reports on the influence of sex on the eradication rate of H. pylori have been published. This study is inconsistent with our results, which may be related to the small sample size of the study. Future studies with large sample sizes are needed for further validation involving humans. Which will include Age, BMI, education level, smoking, drinking, disease status, and history of diabetes of patients with H. pylori.

Conclusion

The efficacy of Annona Senegalese triple therapy for the initial eradication of H. pylori is commendable. These, triple therapy was found to be well tolerated, safe, and economical while avoiding the use of bismuth and its potential adverse events. Therefore, the new triple therapy provides a safe and effective alternative for the initial eradication of H. pylori.

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