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ORIGINAL RESEARCH

Antiulcer Effect of Aqueous Ethanolic Extracts of *Pseudocedrela kotschyi* (Schweinf) Harms (Meliaceae) and *Ximenia americana* L. (Olacaceae)

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Purpose: This study aimed to provide pharmacological evidence of *Pseudocedrela kotschyi* and *Ximenia americana* in preventing or healing peptic ulcers claimed by traditional healers in Burkina Faso.

Methods: The trunk bark of *Pseudocedrela kotschyi* and the roots bark of *Ximenia americana* (Olacaceae) were macerated in mixed ethanol/water (80:20), respectively, to obtain dried extracts. Two models of hydrochloric acid (HCl, 0.3 M/ethanol, 60%) and hypothermic stress-induced peptic ulcer were used. The cytoprotective effect of individual or combined plant extracts was assessed at 1; 10; 30mg/kg. bw. Then, the healing effect of the extracts at 10mg/kg.bw was evaluated within 21 days of treatment on the hydrochloric acid-induced ulcer model. The extracts' antioxidant activity and phenolic content were assessed to support the plant extracts' efficiency.

Results: The extracts of *P. kotschyi* and *X. americana* at 10 mg/kg.bw reduced ulceration index in hydrochloric acid- and hypothermic stress-ulcer models by more than 83% and 65%, respectively. The extract from *X. americana* at 10mg/kg.bw allowed complete ulcer healing but not the association of the two plant extracts. The plant extracts had $IC_{50}$of inhibition of DPPH radical lower than 5µg/mL and total ferric reducing antioxidant power of more than 77 mg EQAA/100mg. The total polyphenolic content was 64.82 ±0.99 and 53.75 ±1.39 mg EGA/g of dried extract of *P. kotschyi* and *X. americana*, respectively.

Conclusion: *X. americana* extract is better than the combined two plant extracts in gastric cytoprotection and ulcer healing. Further investigations are needed to highlight mechanism-based effects.

Keywords: *Pseudocedrela kotschyi*, *Ximenia americana*, aqueous ethanolic extract, antiulcer, antioxidant

Plain Language Summary

This work aimed to provide a scientific base of traditional medicine use of *Pseudocedrela kotschyi* and *Ximenia americana* in peptic ulcer treatment in Burkina Faso. We found that *Ximenia americana*, alone is sufficient to obtain prevention and healing of the peptic ulcer.

Introduction

A peptic ulcer is a gastroduodenal ulcerative disease. It develops in chronic multifactorial conditions spontaneously and by flare-ups. A peptic ulcer consists of a crater evolving from asymptomatic to complicated hemorrhage, stenosis, or perforation lesions.[1] *Helicobacter pylori*, a Gram-negative bacteria, is associated with the genesis and recurrence of peptic ulcer.[2] The imbalance between the defense and repair mechanisms of the gastric lining and aggressive factors such as pepsin and hydrochloric acid is critical.[3] The prevalence of gastric ulcers is estimated at 2% against 8% for duodenal ulcers.[4] In comparison, study reports in Australia and Great Britain showed the prevalence of peptic ulcers between 5.2% and 9.9% in the general population.[5]

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In Africa, peptic ulcer prevalence varies according to the area. Thus, Diarra in Mali, Lawson in Togo, and Ibara in Congo have reported 10.80%, 15.53%, and 30.42%, respectively.[6–8] In Burkina Faso, peptic ulcer was reported in the past decade to represent the third most common of all gastric diseases[9] with an intra-hospital prevalence rate of 6.59%.[10]

The treatment of peptic ulcers consists of anti-secretory, antiulcer medicines and two associated antibiotics curing in the presence of *H. pylori*. The treatment is expensive and takes a more extended period to get healing. In developing countries, traditional healers propose using herbal medicines to treat peptic ulcers. In Burkina Faso, traditional healers use the trunk bark of *Pseudocedrela kotschyi* (Schweinf) Harms (Meliaceae) and *Ximenia americana* (Olacaceae) roots in peptic ulcers. Few data are available to support the use of these plants in the treatment of peptic ulcers. This work aimed to elucidate the pharmacological actions on the manifestations of peptic ulcers.

Materials and Methods

Material

Plants Material

It consisted of the trunk bark of *Pseudocedrela kotschyi* (Schweinf.) Harms (Meliaceae) and the roots bark of *Ximenia americana* L. (Olacaceae) were harvested in Boromo 100 km west of Ouagadougou. Plants specimens were identified by Dr BELEM Maimounata, a botanist searcher at the National Center for Scientific and Technical Research (CNRST), and confirmed by Prof. OUEDRAOGO Amadé. Vouchers of *Pseudocedrela kotschyi* (Schweinf.) Harms (Meliaceae) and *Ximenia americana* L. (Olacaceae) were deposited at the University Joseph KI-ZERBO herbarium under numbers 18024/6984 and 18025/6985, respectively.

Pharmacological Materials

The reagents and the substances used were all analytical grade: lansoprazole (Genpharma, Maroc), isotonic saline solution (Fresenius Kabi, India), and ethanol (Prolabo, France).

Animals

Healthy female mice of the Naval Medical Research Institute (NMRI) strain, three (3) months aged and weighting 30–35 g, were used. They were provided by the International Centre for Research Development on Subhumid Livestock (CIRDES) of Bobo Dioulasso, in the west of Burkina Faso. Mice have raised under 22±1°C temperature and subjected to a cycle of 12 hours of darkness/light. All experiments were conducted by international animal welfare standards as recommended by the European Union on Animal Care (EEC 86/609, UE 2010/63). The protocols were approved by the institutional animal ethical committee of Joseph KI-ZERBO University (CE-UJKZ/2014-04).

Preparation of Extracts

Two hundred grams of powder of each plant were allowed to macerate in an ethanol/water mixture (80:20, v/v) in a proportion of one powder for five parts of solvent at 25°C under magnetic stirring. The extracts were respectively concentrated to dryness in a partial vacuum rotative evaporator (Buchi water bath B-480) at 45°C and left to dry in the oven (Jouan; France). That operation was repeated three times for each plant.

Methods

Total Phenolic and Flavonoid Content

Polyphenols and flavonoid contents in each plant extract using a UV-visible microplate reader spectrophotometer (Epoch 251465, Biotek Instruments, USA).

Total phenolic content determination used the Folin–Ciocalteu reagent method described by Singleton et al.[11] A mixture of extracted samples at different concentrations, Folin–Ciocalteu reagent (1N), and solution of Na_2CO_3 (20%) were incubated for 40 min. Then, the absorbance was read at 760 nm against a control.

Gallic acid was used as a reference compound to produce the standard curve, and the results were expressed as mg of gallic acid equivalents (GAE)/100 g of extract weight.

Total flavonoid content was assessed using the method of Dowd, adapted by Arvouet-Grand et al.[12] In the presence of flavonoids; the aluminum trichloride formed a yellow–green complex with a maximal pick of absorbance at 415 nm. A calibration curve of quercetin allowed the determination of the flavonoid content of extracts.

Assessment of Plant Extracts' Anti-Peptic Ulcer Effect

Two mice models of induced ulcers were used to highlight the cytoprotective effect of plant extracts.

HCl/Ethanol-Induced Peptic Ulcer

A mixture of HCl (0.3 M)/ethanol (60%)-induced peptic ulcer model described by Mizui and Doteuchi[13] was used. Fifty-four female mice were divided into nine groups. Three groups received by an oral route different doses (1, 10, 30 mg/kg. bw) of each aqueous ethanolic extract of *X. americana* or *P. kotschyi*. The reference group received lansoprazole (20 mg/kg.bw). The negative control and the positive control groups received distilled water. Fifty minutes later, except for the negative control group, mice in the other groups received orally 0.2 mL of the mixture of HCl (0.3 M)/ethanol (60%). The negative control group received distilled water. Sixty minutes after administration of the ulcerative agent, the mice were sacrificed under anesthesia with ether vapors.

The stomachs of the mice in different groups were excised and then infused with a 0.9% sodium chloride solution. They were incised following the large curvature and then rinsed with physiological saline solution, after which they were stretched on planks and immersed in 10% formaldehyde solution for 10 minutes. Photographic images of the stomachs of animals were then realized using 12-megapixel resolution camera.

Hypothermic Restraint-Stress-Induced Peptic Ulcer

The method of hypothermic stress-induced ulcer described by Levine was used.[14] Thirty-six mice were divided into six groups. Three test groups received *X. americana*, *P. kotschyi*, and a combination of both extracts at 10 mg/kg.bw. The reference group received lansoprazole (20 mg/kg.bw); the negative and positive control groups received distilled water.

Sixty minutes after the substances were administered, the mice of the test, reference, and positive control groups were immobilized in cylindrical iron cages with ventilation holes and kept at 4 °C for 3 hours. Mice in the negative control group were kept at room temperature. After 3 hours, the mice of the different groups were sacrificed under anesthesia with ether vapors. Then, the stomachs were removed and treated as before.

The images of stomachs from animal groups were analyzed using a computer equipped with ImageJ® software (version 1.43; 2009). The lesions' cumulative area and the stomach's total area were determined, respectively.

The percentage of ulceration (PU) was then calculated according to the formula:

$$PU = \frac{\sum \text{ulceration area}}{\text{stomach area}} x100$$

The percentage of inhibition of ulceration was calculated according to the formula:

$$\%\,\text{of inhibition} = (1 - \frac{PUt}{PUc}) x100$$

PUt: percentage of ulceration in the treated group

PUc: percentage of ulceration in the positive control group.

Assessment of the Healing Effect of Plants Extracts

The model of ulcer obtained by administering 0.2 mL of an HCl (0.3 M)/ethanol mixture (60%) to mice was used. All groups except the negative control group received the mixture. Then, 60 min after the ulcer induction, the test groups received one or combined plant extracts at 10 mg/kg. bw, respectively. Control and reference groups received distilled water or lansoprazole at 20 mg/kg.bw.

The mice of each group, priorly fasted (12h), received individual treatment every 2 days for 21 days. A preliminary study showed the persistence of the lesions after 7 days of treatment. On the 21st day, mice were sacrificed under anesthesia with ether vapors.

The stomachs of animals were opened, rinsed with a physiological saline solution, and fixed in 10% formaldehyde for histological analysis. Prior, macroscopic examination consisted of weighing and palpating stomach pieces was realized.

Then, the area of interest was cut and impregnated in paraffin to allow a thin cross-section. After the paraffin elimination, the pieces were mounted on blades and colored by combining a basic nuclear dye (hematein) with a cytoplasmic dye (eosin). An anatomic pathologist examined and analyzed the blades at magnification 40 on a microscope equipped with a digital camera that allowed the realization of images.

Assessment of Antioxidant Activity

The antiradical activity was evaluated in vitro using the following methods: the 1.1-diphenyl-2-picrylhydrazyl (DPPH) radical reduction test and the Ferric reducing antioxidant power (FRAP) test.

DPPH° Stable Radical Reduction Test

The method described by Blois[15] was used. It is based on reducing the radical DPPH° from dark purple to yellow in the presence of a hydrogen atom donor substance.

The reaction mixture contained 200 µL of 0.004% methanolic DPPH° solution and 10 µL of each plant extract at final concentrations of 30, 10, 3, 1, 0.3, and 0.1 µg/mL following a logarithmic scale.

After 30 minutes of incubation at room temperature without light exposure, the optical density of samples in methanol solution was read at 517 nm against a blank (210 µL of methanol). Negative control contains DPPH° (200 µL) and methanol (10µL). The reference was quercetin. The radical scavenging activity was calculated using the formula:

$$\%\,\text{of inhibition} = \left(\frac{\text{Ac} - \text{As}}{\text{Ac}}\right)\text{x}100$$

Ac: optical density of negative control (maximal OD).

As the Optical Density of the Test Sample

Ferric Reducing Antioxidant Power

The iron-reducing activity of plant extracts allows for assessing their potential antioxidant activity. It was determined using the method described by Hinneburg.[16] It is based on the Fe^{3+}-ion reduction provided by the $K_3[Fe(CN)_6]$ complex. The absorbance of samples was read at a wavelength of 700 nm.

The results were expressed as mean ± ESM of ascorbic acid equivalent/100mg (AAE/100 mg) of extract in repeated triplicate experiences. We used the Student's test for comparing two averages and the one-way ANOVA test with the Bonferroni post-test for comparing several means. The data were processed by PRISM 5.03 software and Microsoft Excel 2010. The significance threshold was $p<0.05$.

Results

Extraction Yield

The maceration procedure allowed a yield of 19.26±0.04% and 22.67±0.02%, respectively, for *P. kotschyi* and *Ximenia americana*. The residual humidity was less than 5% for both extracts.

Total Phenolic and Flavonoids

A calibration curve of gallic acid ($y = 0.0197x + 0.0264$; $R^2 = 0.9948$) allowed the polyphenols content to be determined using the Folin–Ciocalteu method (see Table 1).

Table 1 Total Phenolic and Flavonoid Contents in Aqueous Ethanolic Extracts of *P. kotschyi* and *X. americana*

Aqueous Ethanolic Extracts	Total Phenolic GAE (mg/g of Dried Extract)	Flavonoids QE (mg/g of Dried Extract)
P. kotschyi	64.82 ± 0.99	3.00 ± 0.10***
X. americana	53.75 ± 1.39	0.75 ± 0.02

Notes: ***p<0.0001, *P. kotschyi* versus *X.* americana.
Abbreviations: *P. kostchyi, Pseudocedrela kotschyi; X. americana, Ximenia americana*; GAE, gallic acid equivalent; QE, quercetin equivalent.

The calibration curve of quercetin for total flavonoid content determination was y = 0.0538x – 0.0002; R^2 = 0.9972. The results are presented in Table 1.

Antiulcerogenic Activity

Protective Effects

P. kotschyi and *X. americana* extract at 10 mg/kg.bw dose significantly inhibited ulcer formation at 86.2% (Figure 1) and 83.5%, respectively (Figure 2).

Hypothermic Stress Ulcer

The 10 mg/kg.bw dose of *P. kotschyi* and *X. americana* extracts inhibited ulceration by 65.70% and 95.11%, respectively, compared to the negative control group (Table 2).

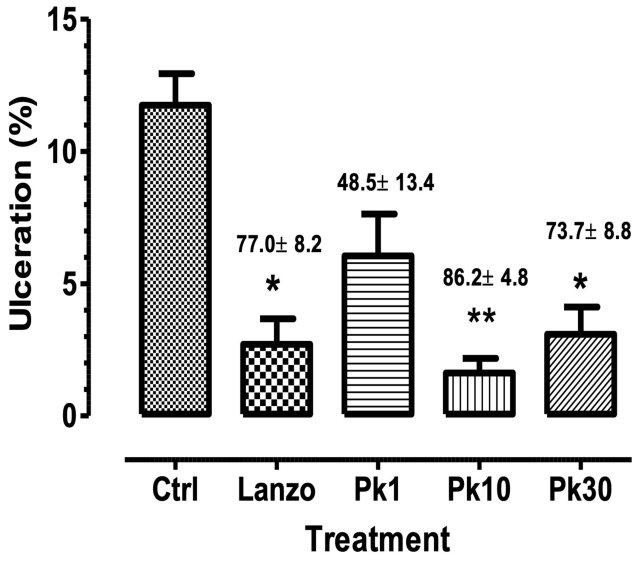

Figure 1 Cytoprotective effect *of P. kotschyi* on hydrochloric acid (0.3 M)/ethanol (60%)-induced ulcer in mice. Pk: *P. kotschyi* at doses 1, 10, 30 mg/kg.bw inhibited respectively 48.5± 13.5; 86.2±4.8; 73.7± 8.8 %, and Lanzo: Lansoprazole**2**0 mg/kg/bw, 70.0 ± 8.2 % compared to Control group. N = 6 mice per group. *p<0.05, ** p< 0.001 vs Control (Ctrl).

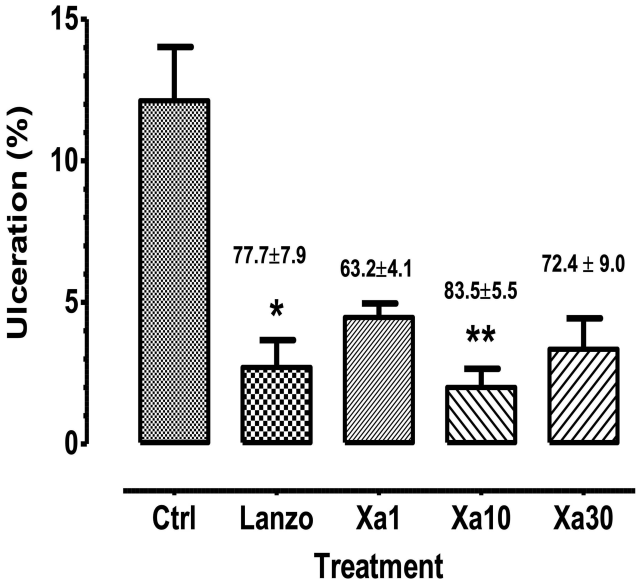

Figure 2 Cytoprotective effect of *X. americana* on hydrochloric acid (0.3 M)/ethanol (60%)-induced ulcer in mice. Xa: *X. americana* at doses 1, 10, 30 mg/kg.bw inhibited respectively 62.2±4.1; 83.5±5.5; 72.4± 9.0 %, and Lanzo: Lansoprazole**2**0 mg/kg/bw, 77.7±7.9 % compared to Control group. N = 6 mice per group; *p<0.05,**p<0.001 vs Control (Ctrl).

Table 2 Cytoprotective Effects of *P. kotschyi* and/or *X. americana* on Hypothermic Stress-Induced Ulcer in Mice

Treatment	Ulceration (%)	Inhibition (%)
Negative control	7.45 ± 0.49	–
Lansoprazole 20 mg/kg.bw	3.42 ± 0.81	54.04 ± 10.87
P. kostchyi 10 mg/kg.bw	2.55 ± 0.65	65.70 ± 8.79
X. americana 10 mg/kg.bw	0.36 ± 0.19 **	95.11 ± 2.51$
P. kotschyi + *X. americana* (10 mg/kg.bw)	1.64 ± 0.54*	77.86 ± 7.18

Notes: n=6 mice/group. *p<0.05; **p<0.002 vs negative control, $ p<0.05 vs lansoprazole-treated group. Histological cuts are representative of the different groups of mice, respectively.
Abbreviations: *P. kostchyi*, *Pseudocedrela kotschyi; X. americana, Ximenia americana.*

The cytoprotective effect of combined extracts at 10 mg/kg.bw dose was better than the individual effect of *P. kotschyi* extract but less than *X. americana* extract effect. The inhibition percentages produced by the extracts are higher than those produced by lansoprazole (Figures 1 and 2).

Healing Power

The extract from *X. americana*, lansoprazole, and mixing of the two extracts at 10 mg/kg.bw dose produced complete regeneration while healing on *P. kotschyi* after 21 days of treatment has a persistent inflammatory reshuffling. The Lansoprazole group yield partial healing (Figure 3).

Plants Extract Antioxidant Activity

DPPH Radical Reduction Test

The inhibition curves of the radical DPPH° based on the concentrations of aqueous ethanolic extracts of trunk bark of *P. kotschyi* and roots bark of *X. americana* allowed the determination of CI50 which are respectively 3.96 and 5.01 versus 1.4 for Quercetin (Figure 4).

Reducing Power Test: FRAP

The reducing power of *P. kotschyi* and *X. americana* extracts was determined against a standard curve of ascorbic acid (y = 0.027x-0.114; R^2 = 0.973). The plant extracts yielded 77.01±2.72 and 77.69±2.06mg EAA/100 mg of dry extract, respectively, for *P. kotschyi* and *X. americana.*

Discussion

This study showed cytoprotective and healing effects of the trunk bark of *Pseudocedrela kotschyi* (Schweinf.) Harms (Meliaceae) and roots bark of *Ximenia americana* L. (Olacaceae) on HCl/Ethanol and hypothermic stress-induced peptic ulcer. Each plant extract or both at 10 mg/kg.bw prevented ulcers induced by cold or acidified ethanol. Healing of the ulcer lesion is obtained in 21 days of treatment with plant extracts versus lansoprazole, an inhibitor of the proton pump of gastric borders cells.

The phytochemical contents of plant extracts are based on biological properties. Previous studies have determined the phytochemical contents of the two plants. Phytochemical screening of the stem bark of *P. kotschyi* retrieved tannins, alkaloids, anthraquinones, saponins, glycosides, flavonoids, and triterpenoids. Three limonoids, highly oxygenated triterpenes with furanyl steroid core structure, and pseudorelone A-B have also been isolated and widely revised.[17] *X. americana* roots bark is reported to contain phenolic, tannins, flavonoids, triterpenes, and fatty acids, the major plant derivatives and the main active ingredients.[18]

Hypothermic stress in mice is reported to activate the vagus nerve[19] and direct vasoconstriction, leading to a decrease in blood flow, mucus production[20,] and an increase in gastrin release.

Flavonoids have good stomach protection by stimulating protective factors such as vasodilation[21] and mucus secretion.[22] *X. americana*[23,24] and *P. kotschyi*[25] are reported to contain flavonoids and polyphenols. At 10 mg/kg. bw, *X. americana* prevented better *P. kotschyi* gastric ulceration (see Table 2). Beyond this qualitative chemical

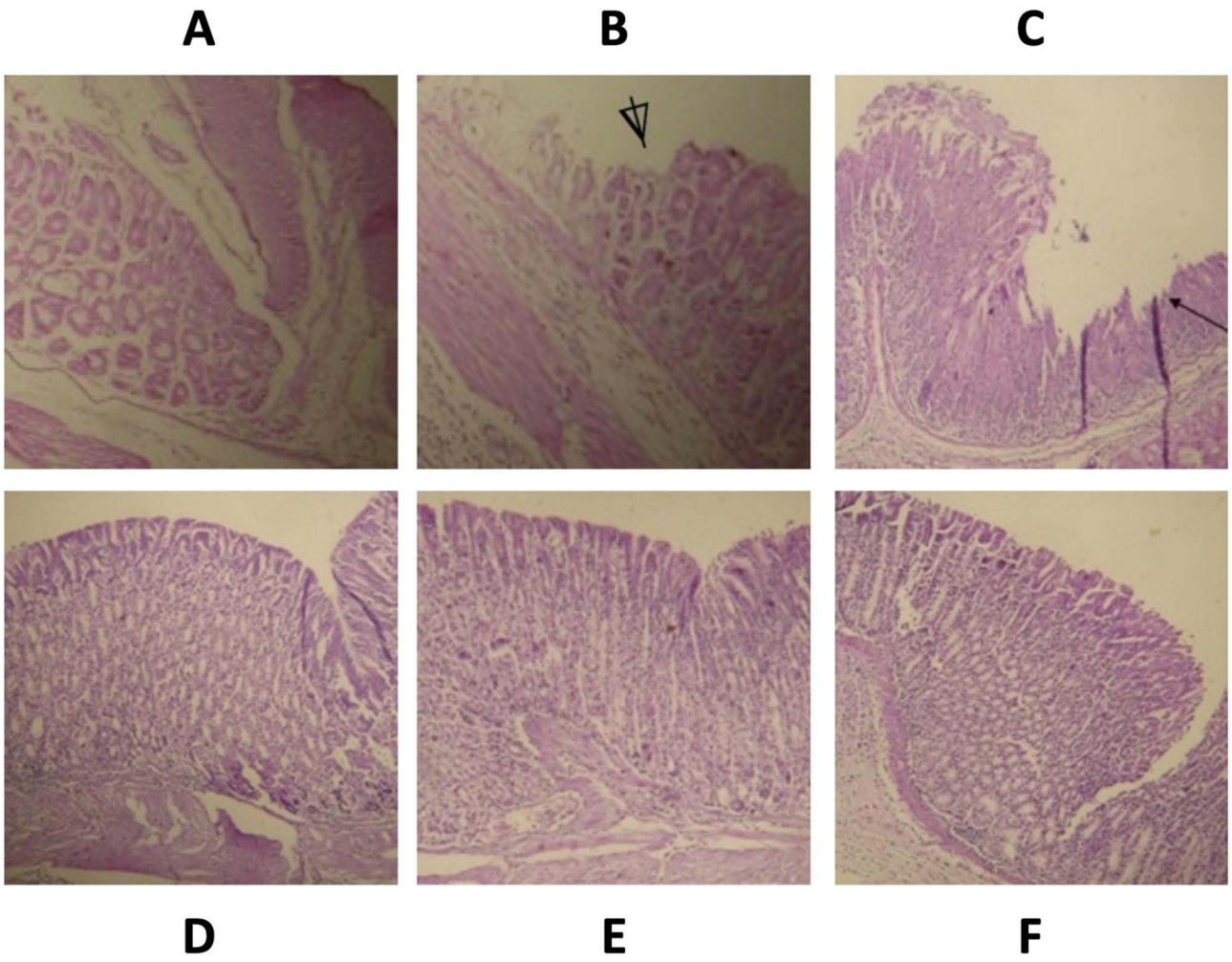

Figure 3 Histological section of mice stomach showing healing effects of *Pseudocedrela kotschyi* and *Ximenia americana* on hydrochloric acid (0.3 M)/ethanol (60%)-induced ulcer (40×; H & E staining). Normal gastric mucosa was observed in distilled water treated (negative control, (**A**)). In hydrochloride acid-challenged groups, ulcerative lesions of the gastric mucosa (⍋) were seen in a positive control (**B**), partial healing mucosa (←) in lansoprazole-treated (**C**); regenerative mucosa were retrieved in group treated with *X. americana* extract (**D**), regenerated inflammatory mucosa in *P. kotschyi*-treated (**E**) and by both plant extracts-treated group (**F**).

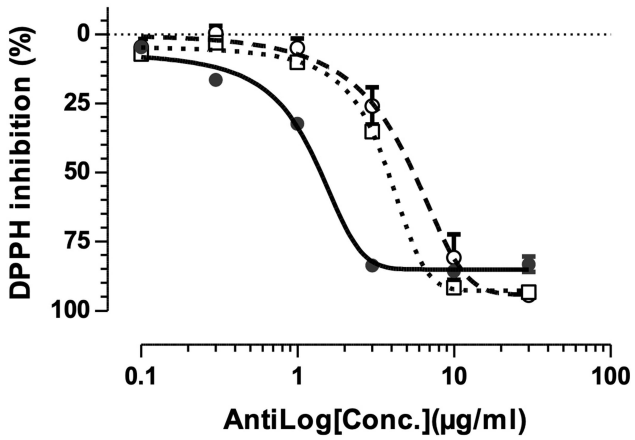

Figure 4 Reduction of radical DPPH by aqueous ethanolic extract of *P. kostchyi* and *X. americana*. Solid line curve and solid circle symbol (quercetin), dotted curve and open square symbol (*P. kotschyi*) and curve in dashed lines and open circle symbol (*X. americana*). Data represent mean ± SEM of two experiences in triplicate; IC_{50} was 1.21± 0.1; 3.60 ± 0.15; 4.11± 1.39 respectively for quercetin, *P. kotschyi*, and *X. americana* extract.

contents of the two plants, other chemical compounds could participate in peptic ulcer prevention. *X. americana* has fewer flavonoids and polyphenol contents but yields a better preventive antiulcer effect than *P. kotschyi*. The anticholinergic activity of plant extracts can reduce chlorohydric acid secretion or increase mucus production and release.

In acidified ethanol-induced lesions, potential mechanisms are solubilizing mucus components, modifying ion movements, and releasing histamine, pepsin, and hydrochloric acid, accelerating the process.[15,24,26] Ethanol also promotes leukocyte recruitment that stimulates inflammatory responses by increasing levels of proinflammatory cytokines such as TNF-α and IL-1β[26,27] and reactive oxygen species (ROS) production.[28] Anti-inflammatory properties have been reported in *X. americana*[29] and *P. kotschyi*.[17] If stopping the inflammatory process is beneficial, at higher doses of plant extracts, a decrease in prostaglandins synthesis is damaging for the gastric mucosa. Parallelly, the blockage of prostaglandins synthesis can promote the synthesis of leukotrienes and other mediators, increasing permeability to ions H^+ and Na^+ and reversing membrane potential.[30]

On the other hand, plant extracts effectively inhibited the radical DPPH° with IC_{50} below 5 µg/mL. The reduction of the radical DPPH° is a widely used test for evaluating the antioxidant activity of active compounds. This test is based on the ability of an active substance to transfer hydrogen or electron atoms to the radical DPPH°.[31] These results show a robust antiradical activity related to polyphenol content.

Reactive oxygen species contribute to the pathogenesis of oxidative stress-related diseases such as cancer, aging, heart failure, and peptic ulcer.[32] In general, plant extracts can mediate anti-peptic ulcer activity by increasing the gastric levels of enzymatic and non-enzymatic antioxidants, namely catalase, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and GSH reductase and reduction of malondialdehyde (MDA) level.[33] Polyphenols, including flavonoids, reported as antioxidants, can participle in the antiulcer activity of the two studied plants. The Ferric Reducing Antioxidant Power (FRAP) test assesses the ability of plant extracts to reduce Fe^{3+} ions in Fe^{2+} ions through electron transfer. The aqueous ethanolic extracts of *P. kotschyi* and *X. americana* showed a high concentration of reducing compounds. There is no difference between the reductive power of the two extracts—the contents of the polyphenolic compounds are almost identical in both plants. Plant polyphenols are predominantly antioxidant substances.[34–36] In addition to polyphenols, several studies reported the antioxidant activity of saponin.[37]

Chronic gastric ulcer healing is favored by gastroprotective, anti-secretory, antioxidant agents, epithelial cell proliferation, and release of prostaglandins. Also, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and their receptors are essential in tissue repair and wounding ulcers. The secondary metabolites like saponins and flavonoids are evoked to be gastroprotective to prevent gastric ulcer complication or healing.[38] The critical content of reducing compounds in both extracts could justify the extracts' protective and healing effect on the induced gastric ulcer. However, there is no synergic effect as the association of the two extracts is not better than that of *X. americana* alone in improving gastroprotective or healing effect.

Conclusion

This study demonstrated the protective and healing effect of the hydroethanolic extract of *P. kotschyi* (Schweinf.) Harms (Meliaceae) and *X. americana* L. (*Olacaceae*) on induced gastric ulcers. These results partially justify plants' traditional use based on active phytochemical compounds and do not yield synergistic effects between plant extracts.

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Disclosure

The authors report no conflicts of interest in this work.

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