Journal of Ayurveda and Integrative Medicine 15 (2024) 100947

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: elsevier.com/locate/jaim

Multi-targeted therapeutic exploration of *Tamarix gallica* flowers for anti-ulcer activity and associated complications

Aakash Kumar Jaiswal [a,1], Yasheshwar [b], Sapna Salar [c], Shamim [d], Dinesh Kumar Yadav [e], Mansi Aggarwal [a,1], Shalini Sharma [f], Rustam Ekbbal [d,1], Gaurav [d,g,*]

[a] School of Pharmaceutical Sciences, IIMT University, O Pocket, Ganga Nagar, 250001, Meerut, Uttar Pradesh, India
[b] Department of Botany, Acharya Narendra Dev College (University of Delhi), Govindpuri, Kalkaji, New Delhi, 110019, India
[c] BBDIT College of Pharmacy, Ghaziabad, 201206, Uttar Pradesh, India
[d] Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O Pocket, Ganga Nagar, 250001, Meerut, Uttar Pradesh, India
[e] Department of Pharmacognosy, SGT College of Pharmacy, SGT University, Gurugram, 122505, Haryana, India
[f] Sunder Deep Pharmacy College, NH-9, Delhi- Meerut Expressway, Dasna, 201002, Ghaziabad, Uttar Pradesh, India
[g] Department of Research and Development, Hamdard Laboratories (India), Factory-B-1/2/3, Industrial Area, Meerut Road, Ghaziabad, 201003, Uttar Pradesh, India

ARTICLE INFO

Keywords:
Peptic ulcer
Tamarix gallica
Aspirin
Network pharmacology
Antioxidant activity
Anti-ulcer activity

ABSTRACT

Background: Peptic ulcer is a condition characterized by open sores resulting from excessive acid production in the stomach or digestive tract, causing damage to the mucosal lining. *Tamarix gallica* (TG), is traditionally known for its anti-inflammatory, antioxidant, antibacterial activity, etc. **Objective:** The scientific evidences based on its efficacy specifically for anti-ulcers activity are limited, hence, the study aimed to evaluate protective effect of TG against aspirin-induced peptic ulcers. **Materials and Methods:** Phytochemical screening was performed followed by assessment of protective effect of TG against aspirin induced toxicity in rats. Network biology and polypharmacology studies were performed to determine the possible molecular targets involved in pathophysiology of ulcers. **Results:** The study revealed that the TG extract at high dose (500 mg/kg b.w.) significantly exhibits protective effect against aspirin induced ulcers via regulation of free acidity pepsin production, overall acidity via regulating antioxidant status (SOD, GSH, CAT, etc). Morphological studies revealed less damage with less disruption of the gastric mucosa layer having normal mucosal structure, no swelling or oedema was found in drug treated groups. **Conclusion:** Moreover, network biology and polypharmacology outcomes revealed that SOD2, CAT, EPO, IL10, EGF, TGFB1 etc. play a significant role in functional gastrointestinal-associated disease or peptic ulcer. Hence, the study concludes that TG polyphenols including phenols and flavonoids play an important role in alleviation of peptic ulcer or associated complication and thus demonstrating TG as a natural therapeutic regimen against ulcers in glance of nature.

1. Introduction

Peptic ulcer disease (PUD) is a prevalent condition that affects around 15% of the population. It is considered as a common result of rising stress levels in daily life. Due to an imbalance between the defensive & aggressive factors that control production of gastric acid, PUD affects the region of GI tract with high conc. of gas increasingly considered the tric acid. It is utmost recurrent GIT ailments, causing patients pain, disturbing their daily routine & causing emotional suffering. H2 receptor antagonists (cimetidine, ranitidine) and PPIs (omeprazole, lansoprazole) may have potential side effects, including gynacomemia and loss of libido [1–3]. It is one of the utmost common GIT problems in experimental practice, and especially widespread in affluent nations. Treatments for ulcers are largely non-specific, focusing on minimising stomach acid production and reinforcing gastric mucosal protection by frequent eating, proper rest, and avoiding ulcerogenic substances like alcohol and cigarettes. Antiacids, proton pump inhibitors, and antihistaminic have all been used to treat ulcers, although the majority of these medications cause a variety of side effects [4–7]. Hence, there is a growing need for more effective and safe anti-ulcer

Peer review under responsibility of Transdisciplinary University, Bangalore.
* Corresponding author.
E-mail address: gautamgaurav878@gmail.com (Gaurav).
[1] **Note:** Authors represented with '$' are equally contributed in the manuscript.

https://doi.org/10.1016/j.jaim.2024.100947
Received 24 March 2023; Received in revised form 3 February 2024; Accepted 8 April 2024
0975-9476/© 2024 The Authors. Published by Elsevier B.V. on behalf of Institute of Transdisciplinary Health Sciences and Technology and World Ayurveda Foundation This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

medications. Recently, there has been a notable surge in interest in natural remedies rooted in the traditional understanding of plant pharmacology. Numerous medicinal herbs have demonstrated gastro-protective properties via encompassing the common causing factors of ulcers like NSAIDs, *H. pylori* infection, medications, etc, and rare causes like anxiety (acute sickness, injuries), chemotherapy, malignancy (gastric/lung cancer, lymphomas), viral infection, Crohn's disease, radiation therapy, vascular insufficiency, and Zollinger's Ellison syndrome. Recognizing and addressing these diverse causes is crucial for developing more targeted and efficient treatments for ulcer management. The exploration of natural remedies and traditional herbal knowledge adds a dimension to the search for safer and more potent anti-ulcer solutions in the ongoing pursuit of improved healthcare [4,8–10]. The second most common cause of PUD is *H. pylori* infection, the use of NSAID & aspirin. The stomach mucosa is frequently protected by prostaglandin secretion. Non-opioids decrease the formation of PGs by inhibiting the COX-1 enzyme, which lowers the production of GI mucus, bicarbonate, and mucosal blood flow [11–13].

Medicinal plants have been acknowledged as a growing therapeutic regimen for peptic ulcer because of least even no side effects of these medications due to the multi-diversity of the chemical components. The disruption of the gastric mucosal defense and repair mechanisms causes ulcers in the stomach or duodenal lining. The stomach ulcer is referred to as a gastric ulcer, while the duodenal ulcer is referred to as a duodenal ulcer, and the two combined are referred to as a peptic ulcer [14–17].

Tamarix gallica (TG) (family: Tamaricaceae) is one of the Indian medicinal plants that has been used for many acute and chronic ailments such as antioxidant, anticancer, hepatoprotective, anti-inflammatory, analgesic, antibacterial, and nephrolithiasis inhibitory effects. The main component of TG is tamarexin, which has shown some positive anti-A aggregation and anti-diabetic effects. It also exhibits anti-hyperlipidemic activity. Various components are present in TG namely polyphenolic compounds like flavonoids like Naringenin, Quercetin, Rhamnetin, Rhamnazin, Tamarixetin, and Kaempferol with other compound phenolic acids, tannins, alkaloids, and glycosides. It is demonstrated that TG is quite safe at doses up to 3000 mg/kg body weight [18–21].

The principal constituent in TG is tamarexin along with polyphenolic compounds such as flavonoids such as Naringenin, Quercetin, Rhamnetin, Rhamnazin, Tamarixetin, Kaempferol with some other compound phenolic acids, tannins alkaloids and glycosides, and has showed some beneficial anti-Aβ aggregation and anti-diabetic effects in-vitro. Additionally, TG was reported to possess multiple pharmacological activities with significant effect as antioxidant and anti-inflammatory. Although, TG is relatively safe at a dose of up to 3000 mg/kg body weight in an acute oral toxicity study [19,20,22].

Taking all these facts into consideration, the study is aimed to explore anti-ulcer activity of a hydro-alcoholic extract of TG flowers in experimental rat model, where ulcers were induced by administrating excess dose of aspirin. Biochemical and morphological and network pharmacology studies were performed to determine multi-targets and therapeutic approaches of TG in anti-ulcer activity.

2. Material and methods

2.1. Chemicals & drugs

All chemicals that were used in this study are of analytical grade, procured from Sunder Deep Pharmacy College Lab & SD-Fine Chemicals Ltd. Mumbai, India. Diagnostic kits for assessment of biochemical parameters & histopathology evaluation were obtained from Erba diagnostic, India. Cytoscape 3.9.1 version software was used to conduct network pharmacology study.

2.2. Plant collection and authentication

The plant drug *Tamarix gallica* (TG) was collected from the local nursery in the month of November. The plant material was authenticated by Department of Botany, CCS University, Meerut, India. The sample specimen was submitted in the institutional laboratory for future prospectus.

2.3. Preparation of extract

The freshly collected flowers of TG was washed away with distilled water to remove dirt and soil. After that plant was dried in shade in aerated place at room temperature. Dry flowers (50 g) were reduced into small pieces & coarse powder by mechanical grinder and then extraction process was conducted using reflux method. A hydroalcoholic solvent (1:1, v/v, 250 ml) was used for extraction for 8 h. After complete extraction, extract was filtered and concentrated under reduced pressure using vacuum rotary evaporator. The extractive yield of the plant material was weighed and stored at room temperature in an air tight closed container [23,24].

2.4. Phytochemical screening of extracts

The phytochemical analysis of hydroalcoholic extract of TG was carried out to identify various chemical constituents (e.g. alkaloids, steroids, phenolic acids, flavonoids, coumarins, terpenoids, carbohydrates, and tannins) as per the reference protocol with some modifications present in the extracts [25–27].

2.5. In-vivo studies for assessment of anti-ulcer activity of Tamarix gallica

2.5.1. Study design

In this study, the choice of animals was used for the experimental study and each animal were divided as per the experimental objectives. A normal control group was taken in the experiment aims to compare a treatment group. A negative control group was used to determine whether a possible changes or difference between groups is caused by drug used for induction of disease. A positive control group is used for possible determination and support the interpretation of other treatment groups (Negative control group and drug treated group).

2.5.2. Experimental animal

Adult Wistar rats weighing 160 ± 20 g were obtained from National Institute of Biologicals, Noida, Uttar Pradesh-201309 for the study. They were kept in Animal House of Sunder Deep Pharmacy College, Ghaziabad. The animals were kept independently in polypro-pylene cages for acclimatization at a 23 ± 2 °C temp. & RH-50–60%, with a 12hr light/dark cycle one week beforehand & during the beginning of experiment. Animal were retained on std. pellet diet & H2O *ad libitum* during housing period. All experimental procedures including rats were shown in accordance with the guidelines of CPCSEA. The protocols of study were approved by the (IAEC) of Sunder Deep Pharmacy College, Ghaziabad, India with approval number **1673/Po/Re/S/12/CPCSEA/2022–8**. Acute toxicity studies were conducted permitting to the OECD guidelines 423 and animals observed for any behavioral and physical changes for 14 days.

2.5.3. Experimental procedure

The study was carried out under controlled environment. A total of 25 animals were divided into five groups and each group contain five animals. Group 1 represented as control group, received normal saline 2 ml/kg/day (p.o.) for 28 days. Group 2 represented as disease control group, received aspirin (in fasted condition) 150 mg/kg/day dissolved in l % CMC in water for first 3 days followed by treatment with normal saline for 28 days. Group 3 represented as standard or positive control group, received Cimetidine (100 mg/kg, p.o.) for 28 days + Aspirin

(150 mg/kg, p.o.) for first 3 days. Group 4 and group 5 represented as drug treated group received TG extract low dose and high dose (250 and 500 mg/kg, p.o.) for 28 days + Aspirin (150 mg/kg, p.o.) for first 3 days, each.

After completion of treatment, each animal was anesthetized using a ketamine and sacrificed via cervical dislocation. Before cervical dislocation, blood samples from each group was collected through direct puncture to the heart for assessment of biochemical studies. The collected blood samples were stored in separate EDTA vial. In order to assess morphological and biochemical parameters, stomach from each rat was collected and released on larger curvature, their gastric contents were combined into straightforward tubes & centrifuged in order to measure several aspects of gastric secretion, including gastric volume, total & free acidity, pH. The condition of the gastric mucosa was assessed to determine the ulcer score, ulcer index, percentage inhibition. Thereafter, the oxidative markers were analysed on homogenates of the stomach tissues [28–31].

2.5.4. Evaluation parameters

Evaluation parameters includes biochemical analysis and antioxidant parameters in which biochemical analysis was done on ulcer index, free acidity, total acidity, pepsin activity and protein content and oxidative parameters such as glutathione (GSH), superoxide dismutases (SODs), catalase (CAT) in serum and malondialdehyde (MDA) formation were determined. The study is performed as per the reference protocol [32–36]. The formula's used to calculate ulcer index and inhibition follows as;

Ulcer Index = Ulcerated area/ Total Stomach Area × 100

$$\%\textbf{Ulcer inhibition} = \frac{[\text{UI. in control} - \text{Ulcer Index in test \& intervention group}] \times 100}{\text{Ulcer Index in control}}$$

2.5.5. Morphological characterization of ulcers

Sample of stomach tissues from each group were morphologically assessed to observe the intensity of ulcers. The intensity of the ulcers on stomach inner part were assessed via directly proportion of wounds on stomach tissue. The images of each stomach tissue were captured for the record purpose [28,29,31].

2.6. Network biology and polypharmacology analysis

Network pharmacology and polypharmacology analysis was performed to determine the possible therapeutic targets to get more effective treatment approaches in alleviation of gastric or peptic ulcers. This analysis was performed as per the reference protocol using Cytoscape software (Version: 3.9.1) and the target protein or biomarkers have been selected based on the present study. CAT, SOD, GSH and MDA and their associated targets were gathered in this analysis and their possible involvement in different pathogenesis was predicted [37,38].

2.7. Statistical analysis

Each group's data was represented as the Mean ± SEM (n = 5). Using Prism Pad software (Version 6.05), the student t-test was used to compare each participant individually before Newman-Keuls test was used to determine degree of significance. Statistically significant was defined as *p < 0.05 while most statistical significance values were expressed as ***p < 0.0001.

3. Results

Extraction process for hydroalcoholic extract of TG was conducted successfully. The extractive yield of TG was found 15.17 ± 0.524 g (w/w) of the sample. the extractive yield was found under the range of ayurvedic pharmacopoeia of India. After extraction, phytochemical screening and in-vivo anti-ulcer activity was performed.

3.1. Phytochemical screening of extracts

Phytochemicals screening of TG extract was performed as per reference protocol, successfully. The outcome of the study showed that alkaloids, steroids, phenolic acids, flavonoids, coumarins, terpenoids, carbohydrates, and tannins were found in hydroalcoholic leaves extracts of TG. Tannins and flavonoids or polyphenols were found significant in the extract while the constituents such as alkaloids, steroids, coumarins etc were found in less extant in the extract.

3.2. In-vivo studies for assessment of anti-ulcer activity of Tamarix gallica

In-vivo anti-ulcer activity of TG was performed as per reference protocol, successfully. biochemical and histopathological examination were assessed to determine protective effect of TG. The parameters such as ulcer index, free acidity index in different study groups, pepsin activity, protein content estimation and anti-oxidant parameters (CAT, SOD, GSH and MDA) evaluated that are followed as.

3.2.1. Ulcer index

The ulcer index at the time of sacrifice was observed macroscopically and noted in each group. The mean ulcer index for each animal was noted down and the drug effect was calculated on the basis of percentage inhibition when compared to standard treated group. In case of % ulceration the negative control was considered as 100% ulceration, for this calculation the negative control will be treated as control for % ulceration inhibition calculation. The results are shown in Table 1.

3.2.2. Free acidity index in different study groups

The free acidity index was calculated in all groups. The free acidity levels were found to improve after dosing of Cimetidine (100 mg/kg b.w.), when standard drug was intervened the free radical index was significantly reduced ($p < 0.05$) in comparison to the disease control group. TG when intervened at low dose level (250 mg/kg) showed a decrease in the free acidity index in comparison to disease control but was found significantly higher while compared to control, a substantial decrease was found. However, free acidity index after the intervention of TG at high dose level (500 mg/kg) was more decreased when compared with disease control group. The outcome of the study has been

Table 1
Estimation of Ulcer Index (units) in different group treated with positive, negative and drug treated groups

Group	Group name	Ulcer index	%Ulcer inhibition
Group 1	Control group	0	NA
Group 2	Disease group	22	0
Group 3	Standard or positive control	5	86
Group 4	TG extract (Low dose)	7	58
Group 5	TG extract (High dose)	6	82

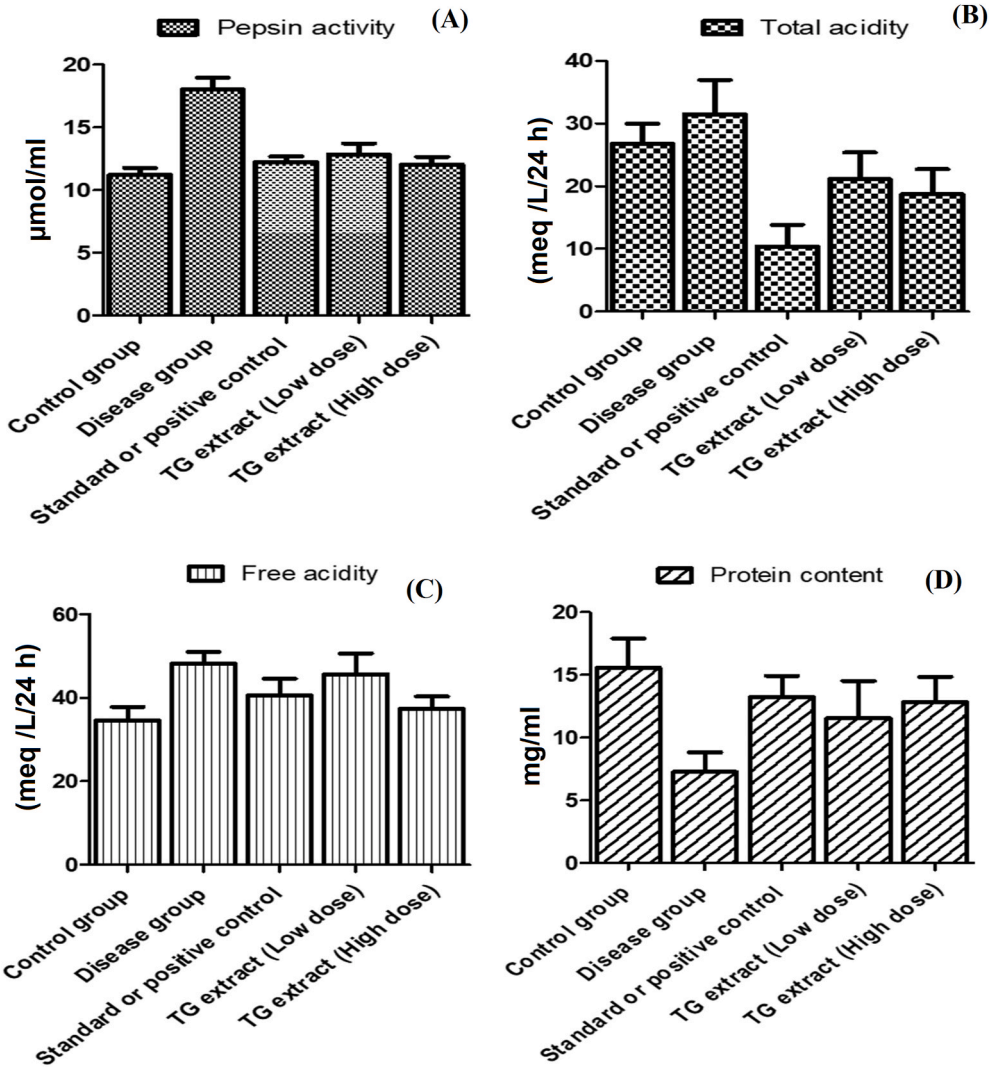

Fig. 1. Graph showing the changes in ulcer profile parameters in different intervention group Free acidity, Pepsin activity, Total acidity, protein content $P < 0.05$ when compared with control $P < 0.05$ when compared with aspirin. (n = 5 animals in each group) Values are shown as mean SEM.

represented in Fig. 1.

3.2.3. *Pepsin activity index in different study groups*

The pepsin activity is an important marker for the pathogenesis of gastric ulcer was studies in the current examination. The levels of pepsin were observed to be significantly increased after aspirin induction in rats while in comparison with non-treated control group, level was found to normalize after the cimetidine intervention, the values were also found to be normalizing in both low and high dose treated group. The outcome of the study has been represented in Fig. 1.

3.2.4. *Protein content estimation in different groups*

A high protein administration is prescribed to give basic amino acids to tissue protein synthesis and in this manner promote healing process. Proteins are additionally included in view of their great buffering activity. The level of protein content was found to be significantly decrease after the aspirin induction in rat when compared with the non-treated group, the level was found to be increased after the cimetidine intervention, the value was also found to be normalize in both low and high dose TG hydroalcoholic extract in treated group. The outcome of the study has been represented in Fig. 1.

3.2.5. *Total acidity index in different study groups*

Total acidity is an important marker to access the gastric ulcer was studied in different groups. The total acidity index was calculated in all groups. The total acidity levels have been reported to be higher after the dosing of aspirin (150 mg/kg), When standard drug i.e. cimetidine was intervened the free radical index was significantly reduced ($p < 0.05$) in comparison to disease control group. *TG* when intervened at low dose level (250 mg/kg) showed decrease in the total acidity index in comparison to disease control but was found significantly higher in comparison to control group, while a substantial decrease was observed in total acidity index after the intervention of *TG* hydroalcoholic extract at high dose level (500 mg/kg) when compared with disease control group. The outcome of the study has been represented in Fig. 1.

3.2.6. *Antioxidant activity*

Anti-oxidant activity was performed to assess protective effect of TG against oxidative stress promoted peptic ulcers induced by aspirin. In this study, stomach tissue homogenate was used to assess the anti-oxidant effect of TG. The outcome of the study was represented statistically that revealed that of *TG* significantly alleviate the oxidative stress in stomach tissue and ameliorates tissue of stomach against lesions via strengthening the anti-oxidative system of enzymes such as CAT, SOD and GSH while significantly ($p < 0.05$*) reduces MDA level in stomach

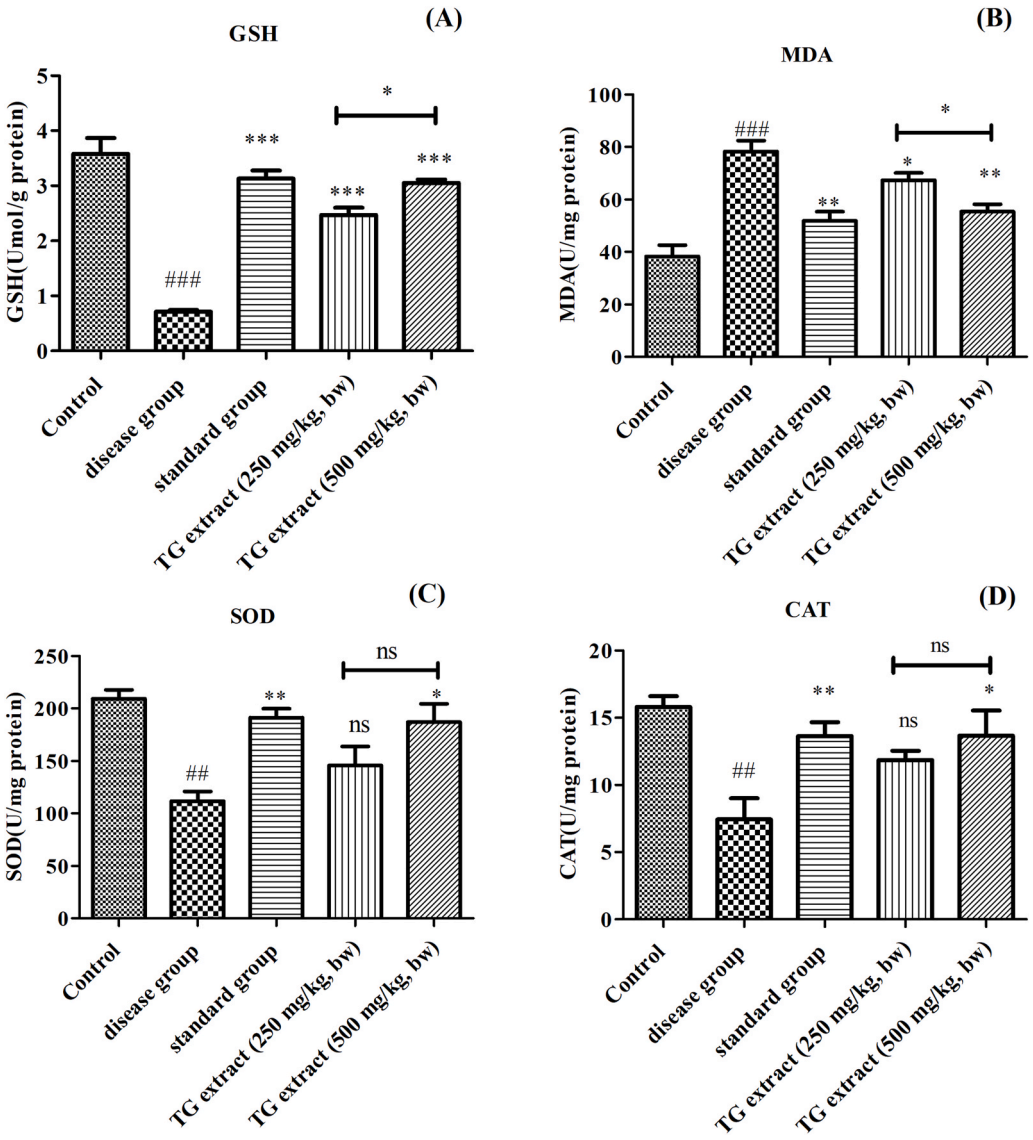

Fig. 2. Anti-oxidant effect of hydroalcoholic extract of … against aspirin induced oxidative stress via regulation of oxidative markers Figure (A) GSH, Figure (B), Figure (C), Figure (D). The data is represented statistically as Mean ± SEM and the significance level were considered at $p < 0.05$. Control group was compared with disease control group while disease control group was compared with drug treated group.

tissue. Comparatively, high dose of the extract exhibited high protection against altered level of oxidative markers via ameliorating the lever of anti-oxidant enzymes such as CAT, SOD and GSH. The outcome of the study has been represented in Fig. 2.

3.2.7. *Morphological characterization of ulcers*

Anti-ulcer activity of *TG* extract was determined to explore its protective effect against aspirin induced ulcers. The effect of drug was determined in two different doses while aspirin was used a negative control to induce ulcers. The results of the study showed that oral administration of aspirin significantly induces ulcers that has been shown with the red color representation in Figure (B) with the marked area. Oral administration of standard drug (Cimetidine; 100 mg/kg, p. o.) significantly alleviates ulcers and showed normal morphology of stomach tissue. In drug samples (extract) treatment or oral administration of extract alleviate the stomach ulcers as it is represented in figure (D and E). However, low dose of extract showed less effect against alleviation of ulcers compared to high dose of the drug. High dose of extract (500 mg/kg, bw) significantly alleviate ulcers formation against adverse effect of aspirin. The outcome of the study has been represented in Fig. 3.

3.3. *Network biology and polypharmacology analysis*

Network pharmacology analysis was conducted to determine multi-targeted and therapeutic approached for treatment of ulcers. For confirmation of possible biomolecular targets in production of ulcers and their regulation, this study was conducted by Cytoscape DisGeNET analysis and the results of the study showed that there are several biomarkers or genomes that are involved in regulation of ulcers, namely SOD2, CAT, EPO, IL10, MIF, GEG, EDN1, LEP, CCK, EGF, TGFB1 etc that play an important role in functional gastrointestinal associated disease. TGFB1 play a role in alleviation of curling ulcers and duodenal ulcers. Peptic ulcers and marginal ulcers are significantly regulated by EDN1 genomic expression. Colitis and stomach diseases significantly induces GI normal function that are possibly occurs due to up or down regulation of GCG. In gastric ulcers, the genes such as EPO, IAPP, ADM, VGF, GHRL, LEP, CAT, CCK and EGF are the most prominent genes that not only

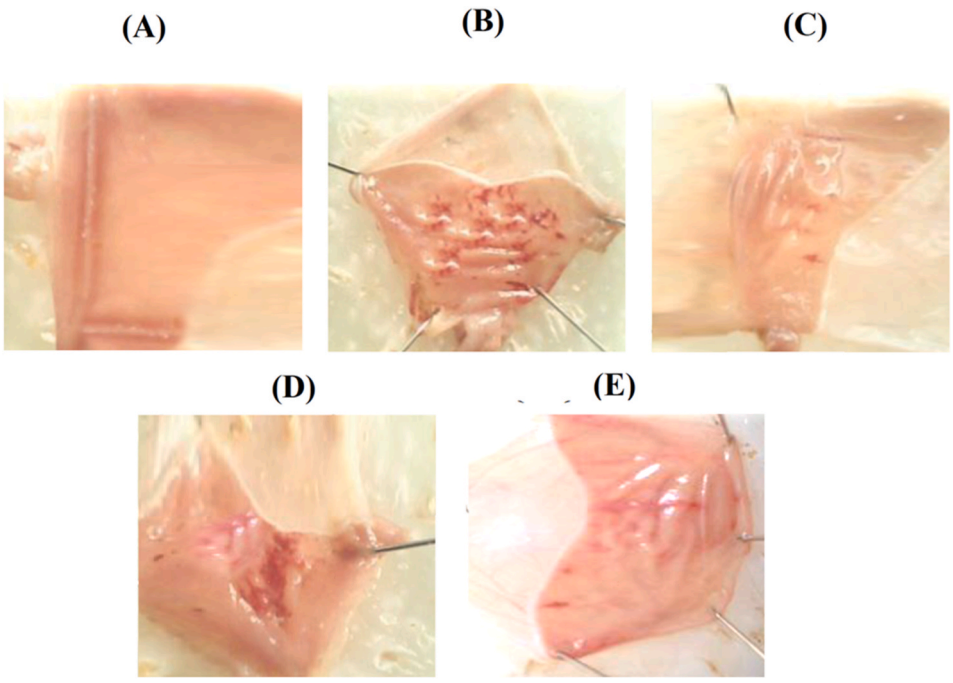

Fig. 3. Morphological assessment of anti-ulcer activity of extract against aspirin induced ulcers in rats. Figure (A) represent normal or control group that showed no destruction in stomach tissue or formation of ulcers. Figure (B) represents the toxic control group or disease control group where high dose of aspirin was administered to induce ulcers and it showed significant induction of ulcers. Orla administration of standard drug (Figure C) showed significant alleviation of ulcers while drug treated groups (Figure D and E) significant ($p < 0.05$) alleviation of ulcers at high dose.

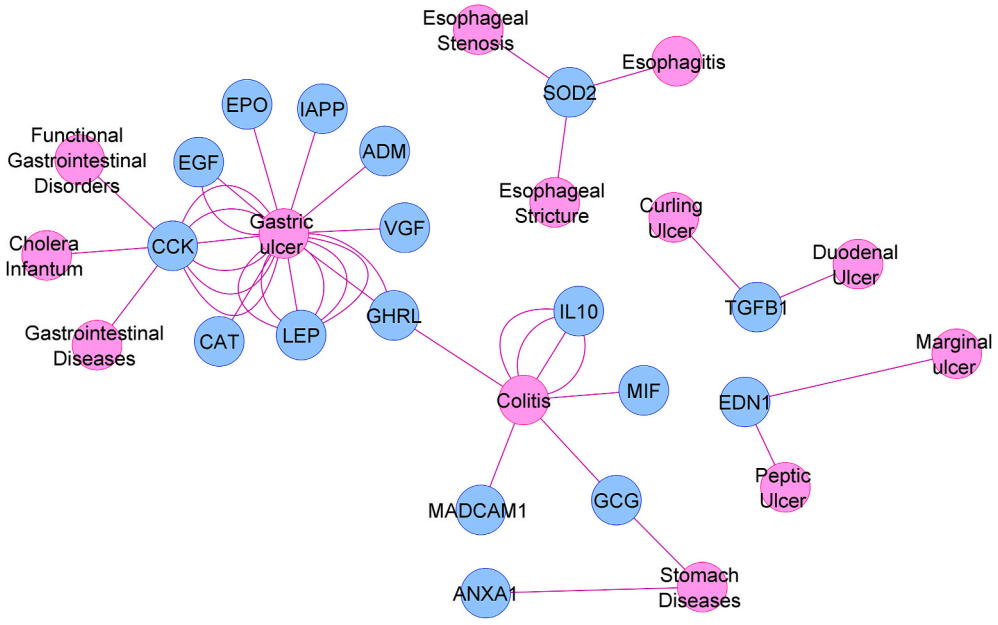

Fig. 4. Gene ontology based DisGeNET analysis was conducted to determine possible targets to determine multi-targeted therapeutic effect for treatment of ulcers. Gene and disease association network involved in ulcer or associated complications represents several genes with sky blue color node while purple color node represents disease group.

involves in gastric ulcers but also GI associated complications such as cholera infantum, functional GI disorders, etc. The gene and disease association network involved in ulcer or associated complications has been depicted in Figs. 4 and 5.

4. Discussion

Medicinal plants are playing an immense role in healthcare system to promoting health and evading disease or disorder, hence contributing as an effective medicinal regimen. *TG* is one of the Indian medicinal plants that has been used since history for treating various acute and chronic disease [19]. Due to lack of ethnopharmacological evidence and molecular mechanism of *TG* against ulcers or anti-ulcer effect, the present aim of the study is associated to validate the anti-ulcer effect of *TG* using in-vivo approaches as well as network pharmacology analysis. In this study, the ulcers were induced in rats by high dose administration of aspirin. Cimetidine was used as standard drug. The drug extract was administered to rats in two different doses (Low: 250 mg/kg and High;

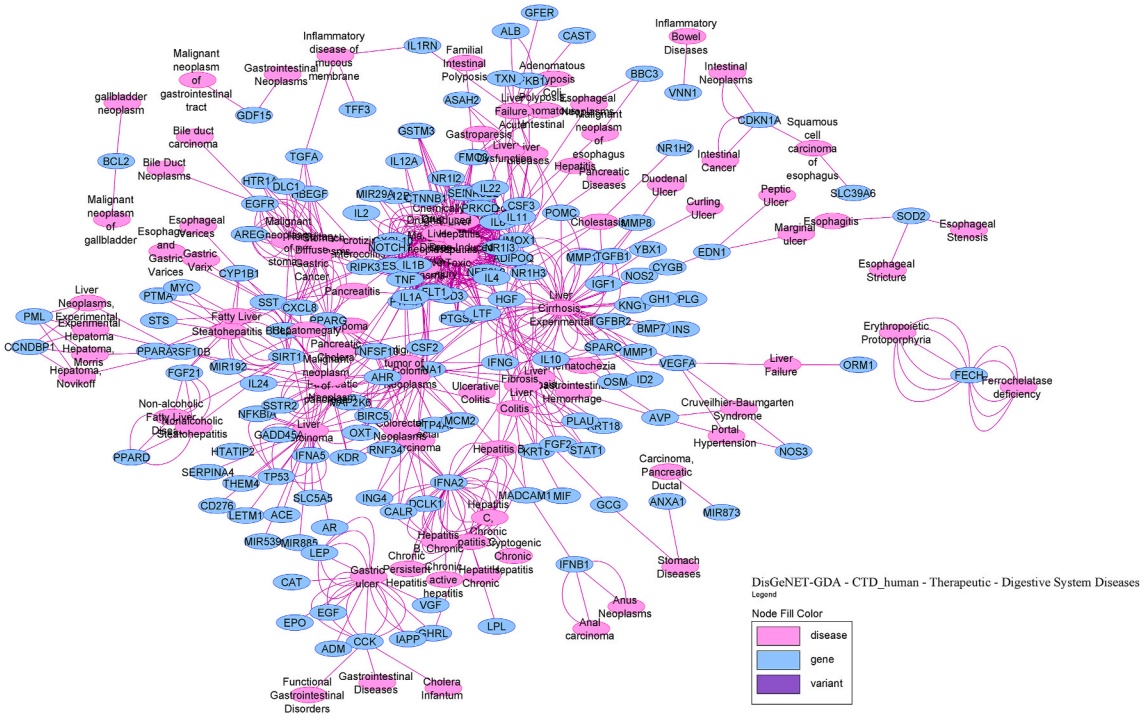

Fig. 5. Developed gene and disease association network with multiple targets involved in ulcer and associated complications.

500 mg/kg). The results of the study showed that aspirin significantly induces the ulcers on stomach tissue that are significantly alleviated after administration of Cimetidine as standard drug as well as *TG* as test drug. low dose of the drug shoed comparatively less effect then its high dose that significantly reduce the ulcers on stomach tissue. Several studies that has been already reported that aspirin significantly induces the stomach ulcers via inhibition of COX-1 activity that creates a propensity state of gastrointestinal ulcers and ulcer complications as well as simultaneously it acts to induce oxidative and inflammatory stress [15,30,39]. Furthermore, it has been demonstrated that natural derived medicine or medicinal plants are a good source of anti-oxidant and anti-inflammatory activity that significantly alleviates oxidative and inflammatory stress via scavenging free radicals and reducing inflammatory cytokines [24,36,38,40].

It has been reported that oxidative stress plays a pivotal role in the pathogenesis of peptic ulcers and gastric carcinoma. Increased reactive oxygen species (ROS) levels contribute to tissue damage and inflammation in the gastrointestinal tract. In peptic ulcers, oxidative stress disrupts the delicate balance between aggressive and defensive factors, exacerbating mucosal injury. Conversely, in gastric carcinoma, chronic oxidative stress can promote carcinogenesis by causing DNA damage and genetic mutations. Antioxidants, crucial in maintaining cellular homeostasis, demonstrate a potential protective role. Understanding the intricate relationship between oxidative stress and antioxidant status is essential for developing targeted therapeutic strategies for both peptic ulcers and gastric carcinoma [41,42].

However, in a study conducted by Tandon et al. (2004) reported that cold restraint stress-induced gastric ulceration in rats showed elevated gastric mucosal LPO and SOD, alongside decreased CAT levels. Similarly, clinical observations in peptic ulcer and gastric carcinoma patients revealed increased serum LPO and a tendency toward decreased SOD and CAT levels. These findings suggest a positive correlation between free radical-induced oxidative stress in both gastric and duodenal ulcers and gastric carcinoma [41].

In a study conducted by Ksouri et al., reported that the flowers of *TG* had stronger antioxidant activity than leaves, with lower IC_{50} values for flower extracts than leaves for lipid peroxidation inhibition ranging from 1.3 (beta-carotene bleaching) to 19 times. Likewise, floral extracts had the greatest total phenolic content (135.35 mgGAE/gDW), and RP-HPLC analysis revealed that the main phenolics were isoquercitin, syringic acid, and catechin. Additionally, when tested against human pathogen strains, Tamarix extracts had notable antibacterial activity. When the concentration rose from 2 to 100 mg/l, the average inhibition zone was from 0 to 6.5 mm. *Escherichia coli* had the lowest activity, whereas Micrococcus luteus displayed the maximum activity. Organ extracts also exhibit a mild to moderate level of efficacy against the tested Candida. According to these results, Tamarix may be a valuable source of antioxidants for the medicinal or nutraceutical businesses as well as food producers [43]. Hmidene et al., reported that that ability of 10 antioxidant flavonoids compound that are isolated form *TG* to prevent amyloid aggregation. The in-vivo and invitro activities were examined for the medicinal halophyte *Tamarix gallica*. In comparison to their aglycone analogues, glucuronosylated flavonoids exhibit comparatively high or significant anti-amyloid (A) and anti-human islet amyloid polypeptide (hIAPP) aggregation action. According to the flavonoids' structure-activity connection, the catechol moiety is crucial for preventing amyloid aggregation, but the methylation of the carboxyl group in the glucuronide moiety and the hydroxyl group in the aglycone flavonoids reduced it [44].

Furthermore, in morphological analysis of stomach tissue that were isolated for different group of rats, it is observed that *TG* high dose significantly alleviates aspirin induced ulcers or tissue injury. However, the effect of *TG* high dose and standard drug showed comparative or no significant difference in their therapeutic effect. Kamada et al., reported that cimetidine significantly reduce the aspirin induced ulcers and restore the normal archeticture of stomuch tissue [45].

Network biology and polypharmacology analysis was conducted to determine the possible targets in alleviation of ulcers or GI associated complications. Tarnawski et al., reported that invading the granulation tissue to rebuild glandular structures inside the ulcer scar, epithelial cells multiply and move into the ulcer margin to cover (reepithelialize) the ulcer [29,46]. Growth factors, including trefoil peptides, EGF, its receptor (HGF and Cox2), HGF, bFGF, and PDGF, as well as locally generated cytokines, regulate the reepithelialization and rebuilding of

glandular structures by regenerating cells in an organized and integrated manner to assure the quality of mucosal regeneration [47]. Certain growth factors, most notably EGF, activate transcription factors and cell proliferation after moving to the nucleus via signal transduction pathways including EGF-R, MAP (Erk1/Erk2) kinases, adaptor proteins (Shc, Grb2, and Sos), Raf1, and Ras. Growth factors regulate cell migration through the Rho/Rac and signalling pathways including PLC-gamma, PI-3 K, and phosphorylation of focal adhesion proteins. Cell migration also necessitates cytoskeletal rearrangements. The base of the ulcer produces granulation tissue. It is made up of connective tissue cells like fibroblasts, macrophages, and proliferating endothelial cells that form microvessels under the control of angiogenic growth factors like bFGF, VEGF, and angiopoietins. These factors are all necessary for the restoration of the microvascular network in the mucosa, which is essential for the supply of oxygen and nutrients. Hypoxia, which stimulates hypoxia-inducible factor, which binds to the VEGF promoter, appears to be the main mechanism of angiogenic growth factor activation and the production of their receptors [48], [49].

5. Conclusion

The hydro-alcoholic extract of *TG* flowers revealed possible anti-ulcer efficacy against aspirin induced ulcer. In all metrics, the extract's activity was compared to that of the Standard drug, demonstrating that it significantly suppresses proton pump activity. Based on the current findings and available information, it can be stated that *Tamarix gallica's* anti-ulcer effect is mostly attributable for the regulation of defensive factors via improved stomach cyto-protection and partly due to acid inhibition. The high dose of *TG* flower extract significantly suppress aspirin induced ulcers lesions than its low dose. The future directions for accelerating and improving ulcer or wound healing by *TG* or isolated active principles can target the gene and protein therapy approaches with growth factors specially EGF, HGF Cox2, HGF, bFGF, and PDGF, their combinations, and the use of stem cells and tissue engineering. These limitations can be overcomed by using combinatorial protein engineering to improve growth factor stability, and increase GF expression, biodistribution, and tissue half-lives; or by altering their cell or receptor binding affinity.

Funding sources

There is no funding available to conduct this study.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

AKJ: Conceptualization, Methodology, Software, Formal Analysis, Investigation, Resources, Writing Original Draft, Visualization, **MA**: Methodology, Data Curation, Visualization and Acquisition, **NS**: Methodology, Formal Analysis, Investigation, **RE:** Software, Writing Original Draft, Review and Editing, Visualization, Supervision, Acquisition **SK:** Formal Analysis, Data Curation, Supervision, **SS:** Validation, Investigation, Review and Editing, **G:** Conceptualization, Software, Validation, Resources, Review and Editing, Supervision, Acquisition.

Acknowledgement

Authors would like to acknowledged Sunder Deep Pharmacy College, Ghaziabad-201015, Uttar Pradesh, India; and Department of Pharmacy, IIMT University, O Pocket, Ganga Nagar, Meerut, Uttar Pradesh 250001 for providing facilities to conduct and complete the study, smoothly.

References

[1] Gelan M, Eba A, Nigatu D, Amsalu B. Peptic ulcer disease: a cross-sectional study of symptoms and risk factors among students at Jimma University, Ethiopia. Gastrointest Nurs 2021;19(2):36–40. https://doi.org/10.12968/gasn.2021.19.2.36.

[2] Murthy Dvss N, Chakravarthy DYK, Rao Dy V. Estimation of anti-ulcer activity of aqueous extracts from the leaves of nyctanthes arbortristis on albino rats. Ann Trop Med Publ Health 2020. https://doi.org/10.36295/asro.2020.231939.

[3] Usman M, Malik S, Zafar A. Finding the risk factors responsible for peptic ulcer disease among patients visiting Jinnah Hospital Lahore. Indo Am J Pharm Sci 2018;5(5):3268–79.

[4] Kotha A, Aswath Kumar V, Kagalipura VG. A study on surgical complications of peptic ulcer disease: a prospective study at a tertiary care center. Int Surg J 2020;7(2):408–13. https://doi.org/10.18203/2349-2902.isj20200288.

[5] Mak K-K, Kamal M, Ayuba S, Sakirolla R, Kang Y-B, Mohandas K, et al. A comprehensive review on eugenol's antimicrobial properties and industry applications: a transformation from ethnomedicine to industry. Pharm Rev 2019;13(25):1–9. https://doi.org/10.4103/phrev.phrev_46_18.

[6] Lukáš M. Therapy for peptic ulcer disease. Vnitr Lek 2018. https://doi.org/10.36290/VNL.2018.082.

[7] Vimala G, Gricilda Shoba F. A review on antiulcer activity of few indian medicinal plants. J Microbiol 2014. https://doi.org/10.1155/2014/519590.

[8] Nihar Ranjan K, Shreechandan P, Priyadarshini P, Sabhya Sampad S. Herbal drugs in treatment of peptic ulcer. May Ed |wwwJbinoCom | Innov Assoc JBio 2017.

[9] Chew Y-L. The beneficial properties of virgin coconut oil in management of atopic dermatitis. Phcog Rev 2019;13:24–7.

[10] Osadchuk AM, Davydkin IL, Gricenko T, Osadchuk MA. General and particular issues of etiopathogenesis of peptic ulcer and gastric cancer: current status of the problem. Ter Arkh 2020. https://doi.org/10.26442/00403660.2020.02.000485.

[11] Fashner J, Gitu AC. Diagnosis and treatment of peptic ulcer disease and H. pylori infection. Am Fam Physician. 2015;91(4):236–42.

[12] Xia B, Xia HHX, Ma CW, Wong KW, Fung FMY, Hui CK, et al. Trends in the prevalence of peptic ulcer disease and Helicobacter pylori infection in family physician-referred uninvestigated dyspeptic patients in Hong Kong. Aliment Pharmacol Ther 2005. https://doi.org/10.1111/j.1365-2036.2005.02554.x.

[13] Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002;359(9300):14–22. https://doi.org/10.1016/S0140-6736(02)07273-2.

[14] Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, Smolic M. Peptic ulcer disease: a brief review of conventional therapy and herbal treatment options. J Clin Med 2019;8(2):179. https://doi.org/10.3390/jcm8020179.

[15] Boakye-Yiadom M, Kumadoh D, Adase E, Woode E. Medicinal plants with prospective benefits in the management of peptic ulcer diseases in Ghana. BioMed Res Int 2021;2021:5574041. https://doi.org/10.1155/2021/5574041.

[16] Awaad AS, El-Meligy RM, Soliman GA. Natural products in treatment of ulcerative colitis and peptic ulcer. J Saudi Chem Soc 2013. https://doi.org/10.1016/j.jscs.2012.03.002.

[17] Kumadoh D, Archer MA, Yeboah GN, Kyene MO, Boakye-Yiadom M, Adi-Dako O, et al. A review on anti-peptic ulcer activities of medicinal plants used in the formulation of Enterica, Dyspepsia and NPK 500 capsules. Heliyon 2021:12345. https://doi.org/10.1016/j.heliyon.2021.e08465.

[18] Lefahal M, Benahmed M, Louaar S, Zallagui A, Duddeck H, Medjroubi K, et al. Antimicrobial activity of Tamarix gallica L. Extracts and isolated flavonoids. Adv Nat Appl Sci 2010;4:289–92.

[19] Salissou MTM, Mahaman YAR, Zhu F, Huang F, Wang Y, Xu Z, et al. Methanolic extract of Tamarix Gallica attenuates hyperhomocysteinemia induced AD-like pathology and cognitive impairments in rats. Aging (Albany NY) 2018;10(11):3229–48. https://doi.org/10.18632/aging.101627.

[20] Terrones A, Juan A. Seventeen new microsatellites for Tamarix gallica and cross-amplification in Tamarix species. Appl Plant Sci 2020;8(1):e11317. https://doi.org/10.1002/aps3.11317.

[21] Urfi MK, Mujahid M, Badruddeen B, Rahman MA, Rahman MA. The role of tamarix gallica leaves extract in liver injury induced by rifampicin plus isoniazid in sprague dawley rats. J Diet Suppl 2018;15(1):24–33. https://doi.org/10.1080/19390211.2017.1310783.

[22] Chaturvedi S, Drabu S, Sharma M. Anti- inflammatory and analgesic activity of Tamarix gallica. Int J Pharm Pharmaceut Sci 2012;4:653–8.

[23] Gaurav Khan MU, Basist P, Zahiruddin S, Ibrahim M, Parveen R, et al. Nephroprotective potential of Boerhaavia diffusa and Tinospora cordifolia herbal combination against diclofenac induced nephrotoxicity. South Afr J Bot 2022:238–47. https://doi.org/10.1016/j.sajb.2022.01.038. 000.

[24] Khan A, Zahiruddin S, Ibrahim M, Basist P, Gaurav Parveen R, et al. Thin layer chromatography-mass spectrometry bioautographic identification of free radical scavenging compounds and metabolomic profile of Carica papaya linn. fruit and seeds using high-performance thin-layer chromatography, gas chromatography-mass spectro. Phcog Mag 2021;17(05):s21–8. https://doi.org/10.4103/pm.pm_326_20.

[25] Abeysinghe DT, Kumara KAH, Kaushalya KAD, Chandrika UG, Alwis DDDH. Phytochemical screening, total polyphenol, flavonoid content, in vitro antioxidant and antibacterial activities of Sri Lankan varieties of Murraya koenigii and Micromelum minutum leaves. Heliyon 2021:12345. https://doi.org/10.1016/j.heliyon.2021.e07449.

[26] Hossain MA, Al-Raqmi KAS, Al-Mijizy ZH, Weli AM, Al-Riyami Q. Study of total phenol, flavonoids contents and phytochemical screening of various leaves crude

extracts of locally grown Thymus vulgaris. Asian Pac J Trop Biomed 2013;3(9):705–10. https://doi.org/10.1016/S2221-1691(13)60142-2.
[27] Hayat J, Akodad M, Moumen A, Baghour M, Skalli A, Ezrari S, et al. Phytochemical screening, polyphenols, flavonoids and tannin content, antioxidant activities and FTIR characterization of Marrubium vulgare L. from 2 different localities of Northeast of Morocco. Heliyon 2020:12345. https://doi.org/10.1016/j.heliyon.2020.e05609.
[28] Obasi NA, Aloke C, Obasi SE, Egwu CO, Famurewa AC, Ogbu PN. Protective effects of dialium guineense pulp on aspirin-induced gastric mucosal injury in albino rats. J Appl Biomed 2021;19(3):170–8. https://doi.org/10.32725/jab.2021.015.
[29] Panda V, Sonkamble M. Anti-ulcer activity of Ipomoea batatas tubers (sweet potato). Funct Foods Heal Dis 2012;2:48–61. https://doi.org/10.31989/ffhd.v2i3.99.
[30] Wang Z, Hasegawa J, Wang X, Matsuda A, Tokuda T, Miura N, et al. Protective effects of ginger against aspirin-induced gastric ulcers in rats. Yonago Acta Med. 2011;54(1):11–9.
[31] Verma VK, Singh N, Saxena P, Singh R. Anti-ulcer and antioxidant activity of moringa oleifera (Lam) leaves against aspirin and ethanol induced gastric ulcer in rats. Res J Pharmacol 2012;2(2):46–57.
[32] Pal S, Chaudhuri AKN. Studies on the anti-ulcer activity of a Bryophyllum pinnatum leaf extract in experimental animals. J Ethnopharmacol 1991;33(1–2):97–102. https://doi.org/10.1016/0378-8741(91)90168-D.
[33] Bag P, Ojha D, Mukherjee H, Halder UC, Mondal S, Biswas A, et al. A dihydropyrido-indole potently inhibits HSV-1 infection by interfering the viral immediate early transcriptional events. Antivir Res 2014;105:126–34. https://doi.org/10.1016/j.antiviral.2014.02.007.
[34] Verma S, Kumar VL. Artesunate affords protection against aspirin–induced gastric injury by targeting oxidative stress and proinflammatory signaling. Pharmacol Rep 2018;70(2):390–7. https://doi.org/10.1016/j.pharep.2017.06.003.
[35] Ansari MA, Iqubal A, Ekbbal R, Haque SE. Effects of nimodipine, vinpocetine and their combination on isoproterenol-induced myocardial infarction in rats. Biomed Pharmacother 2019;109:1372–80. https://doi.org/10.1016/j.biopha.2018.10.199.
[36] Ekbbal R, Iqubal A, Ansari M, Ahmad S, Haque S. Evaluation of cardioprotective potential of isolated swerchirin against the isoproterenol-induced cardiotoxicity in wistar albino rats. Phcog Mag 2022;18:10. https://doi.org/10.4103/pm.pm_500_20.
[37] Gaurav. GC–MS metabolomics and network pharmacology-based investigation of molecular mechanism of identified metabolites from Tinospora cordifolia (Willd.) miers for the treatment of kidney diseases. Phcog Mag 2022;18:548–58. https://doi.org/10.4103/pm.pm_582_21.
[38] Gautam G. Network pharmacology-based validation of traditional therapeutic claim of momordica charantiain alleviating diabetic nephropathy, vol. 1; 2022. p. 1–10.
[39] Mitra P, Ghosh T, Kumar Mitra P. Anti gastric ulcer activity of Amaranthus spinosus linn. Leaves in aspirin induced gastric ulcer in rats and the underlying mechanism. SMU Med J 2014;1(2):313–28.
[40] Khan MU, Gaurav Zahiruddin S, Basist P, Krishnan A, Parveen R, et al. Nephroprotective potential of Sharbat-e-Bazoori Motadil (sugar-free) in HEK-293 cells and Wistar rats against cisplatin induced nephrotoxicity. J King Saud Univ Sci 2022;34:101839. https://doi.org/10.1016/j.jksus.2022.101839.
[41] Ksouri R, Falleh H, Megdiche W, Trabelsi N, Mhamdi B, Chaieb K, et al. Antioxidant and antimicrobial activities of the edible medicinal halophyte Tamarix gallica L. and related polyphenolic constituents. Food Chem Toxicol 2009;47(8):2083–91. https://doi.org/10.1016/j.fct.2009.05.040.
[42] Hmidene A Ben, Hanaki M, Murakami K, Irie K, Isoda H, Shigemori H. Inhibitory activities of antioxidant flavonoids from tamarix gallica on amyloid aggregation related to Alzheimer's and type 2 diabetes diseases. Biol Pharm Bull 2017;40(2):238–41. https://doi.org/10.1248/bpb.b16-00801.
[43] Kamada T, Satoh K, Itoh T, Ito M, Iwamoto J, Okimoto T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2020. J Gastroenterol 2021;56(4):303–22. https://doi.org/10.1007/s00535-021-01769-0.
[44] Thorat YS, Sarvagod AM, Kulkarni SV, Hosmani AH. Treatment of mouth ulcer by curcumin loaded thermoreversible mucoadhesive gel: a technical note. Int J Pharm Pharmaceut Sci 2015;7:399–402.
[45] Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. Dig Dis Sci 2005;50(Suppl 1):S24–33. https://doi.org/10.1007/s10620-005-2803-6.
[46] Tarnawski A. Molecular mechanisms of ulcer healing. Drug News Perspect 2000;13(3):158–68. https://doi.org/10.1358/dnp.2000.13.3.858438.
[47] Tarnawski AS, Ahluwalia A. The critical role of growth factors in gastric ulcer healing: the cellular and molecular mechanisms and potential clinical implications. Cells 2021;10(8):1964. https://doi.org/10.3390/cells10081964.