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Review Paper

Gastroprotective potential of *Phoenix dactylifera* fruit in ethanol-induced gastric ulceration in rats: A systematic review of preclinical evidence and mechanistic insights

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ABSTRACT

Gastric ulcer is an overriding gastrointestinal condition that is responsible of mucosal erosion due to the failure in maintaining balance between predisposing factors and defense mechanism. Gastric injury induced by ethanol is broadly regarded as a preclinical system to examine the mucosal damage caused by oxidative stress and to test possible gastroprotective drugs. Phoenix dactylifera is a date fruit that is known to be high in phenolic compounds, flavonoids, vitamins, and minerals with proven antioxidant and anti-inflammatory effects. The purpose of this systematic review was to obtain the preclinical evidence on the gastroprotective effect of Phoenix dactylifera fruit against the gastric ulcer disease caused by ethanol in rat model and to clarify the mechanisms of the effect. An extensive literature search has been performed in key electronic databases according to PRISMA. Included studies were in vivo rat studies assessing fruit-derived extracts versus ethanol induced injury to the gastric mucosa in which ulcer parameters and biochemical indicators were quantitatively measured. The results always showed high levels of decrease in the ulcer index, lesion area, and histopathological damage after Phoenix dactylifera extracts. Protective activities were also dose-dependent and in some studies even comparable with conventional antiulcer drugs. Mechanically, presence of the fruit extracts inactivated the oxidative stress through

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decreasing the level of malondialdehyde and recovery of the endogenous antioxidant enzymes; superoxide dismutase, catalase and reduced glutathione. Also, there were inhibition of pro-inflammatory cytokine and maintenance of mucosal integrity. Although there has been variability in methodology across studies, the general finding is there is a multifactorial role of gastroprotection that is mediated by using antioxidant and anti-inflammatory mechanisms as a central means. Translational applicability requires further standardized experimental studies and clinical testing to support its validation.

INTRODUCTION

Gastric ulcer has remained a key issue in the world health with its presentation being one of the most common forms of the peptic ulcer disease (PUD). It is defined by local mucosal injury which goes across the muscularis mucosa into deeper on the gastric wall[1]. The gastric ulceration pathogenesis is a complex of deficit of aggressive factors, such as gastric acid, pepsin, reactive oxygen species (ROS), alcohol use, nonsteroidal anti-inflammatory drugs (NSAIDs), stress, and *Helicobacter pylori* infection, and protective processes, such as mucus secretion, bicarbonate production, prostaglandin production, mucosal blood flow, and epithelial regeneration[2]. In case of the break of the protective barrier of the gastric mucosa, the effect of the exposure to acidic gastric contents is tissue erosion, inflammation, and ulcer. Although effective pharmacotherapies, such as proton pump inhibitors (PPIs), H₂ receptor antagonists, cytoprotective agents, and *H. pylori* eradication using antibiotics, are available, gastric ulcers still remain a therapeutic challenge[3]. The side effects of long-term use of PPIs include nutrient malabsorption, predisposition to infection, and possible tissue renal and

cardiovascular risks. In addition, the recurrence rates are also high especially among people who are at risk of constant exposure to factors like alcohol consumption and NSAID use. These constraints have triggered increased interest in the alternative and complementary therapeutic approaches, especially those based on multi-targeted multi-mechanism natural product derived. Inflammation and oxidative stress are in the spotlight of the pathogenesis and evolution of gastric ulcers. Improper generation of ROS causes lipid peroxidation, protein oxidation, and DNA damage in the gastric mucosal cells. Oxidative damage biomarkers, like malondialdehyde (MDA) and endogenous defense mechanisms, such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), are endogenous antioxidant systems[4]. The imbalance of this oxidative mechanism leads to the vulnerability of the mucosa. At the same time, tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β) and cyclooxygenase-2 (COX-2) are inflammatory factors that enhance tissue damage and slow down healing. Because of the multifactorial pathogenesis of gastric ulceration, protective effects of therapeutic agents with antioxidant, anti-inflammatory, cytoprotective and mucosal regenerative capabilities could be more beneficial. In this regard, medicinal plants and nutritional functional foods have become more and more popular as possible gastroprotective agents. The study of bioactive materials of plant origin is part of the overall trend of evidence-based authentication of traditional medicines and ethnopharmacology[5].



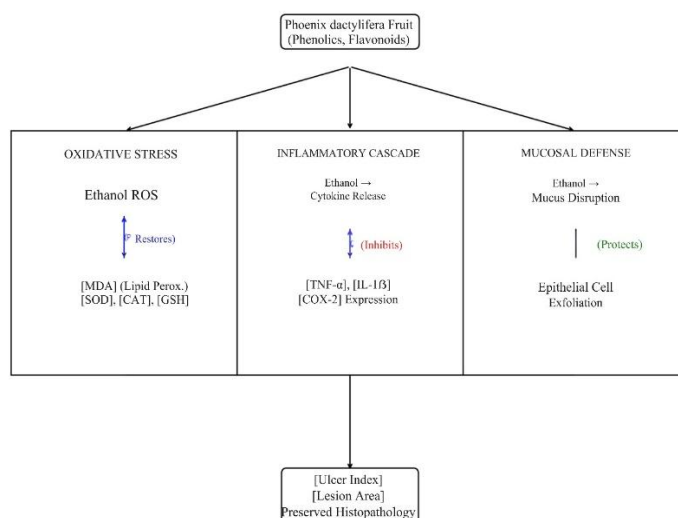


Fig: 1 Mechanism insights *Phoenix dactylifera*

Ethanol induced ulcer model

The ethanol-induced gastric ulcer model in rats is among experimental models that have been widely adopted to study gastric ulceration, because of its reproducibility, simplicity and applicability to the occurrence of oxidative stress-mediated mucosal injury. Administration of ethanol causes rapid and direct harm of the gastric mucosa, which resembles that of acute gastric injury in man following excessive alcohol intake[6][7]. This model is specifically useful in the assessment of cytoprotective and antioxidant activities of potential therapeutic agents. Pathophysiology of the ethanol-induced gastric injury is a series of several processes that are interrelated. Ethanol interferes with the gastric mucosal barrier by dissolving mucus and phospholipids thus elevating mucosal permeability. This interruption enables the rise of the hydrogen ions into the epithelial lining consequently causing intracellular acidosis and necrosis of the cells. Vascular damage is also caused by ethanol, resulting in decreased blood flow in the gastric mucosa and ischemia that only adds to tissue damage. Oxidative stress is a key element of the ulcerogenesis caused by ethanol. Ethanol metabolism produces too much ROS, superoxide anions, hydroxyl radicals, and

hydrogen peroxide[8][9]. These radical species trigger lipid peroxidation, destabilize cellular membrane and disrupts mitochondrial activity. Oxidative imbalance is always evident in this model as a result of high levels of MDA and low activities of antioxidant enzymes. Additionally, ethanol triggers inflammatory pathways, enhancing the production of pro-inflammatory cytokines and inflammation of neutrophils into the gastric mucosa. These inflammatory events play a role in edema, hemorrhage and erosion of epithelial surface. Ethanol exposure causes widespread mucosal lesions by the exfoliation of epithelial cells, submucosal edema, hemorrhage streaks and inflammatory cell infiltration and is histopathologically characterized. The efficacy of therapeutic intervention is usually measured using quantitative parameters, including ulcer index, area of lesion, and percentage of ulceration inhibition which are used in preclinical studies. The ulcer model induced by ethanol is specifically an appropriate test to screen the natural products because it is sensitive to antioxidant and cytoprotective action. Mucus-stimulating agents, antioxidant enzyme replacement agents, inflammatory mediator inhibitors, and microcirculatory preservatives have been shown to

have potent ulcer prevention in this model. Hence, it offers a mechanistic platform by which the plant derived compounds that have the potential of being gastro protective can be evaluated[10][11].

Rationale for *Phoenix dactylifera*

Date palm, *Phoenix dactylifera* L. is a fruit with high nutritional value that has been extensively grown in the Middle East, North Africa, and some parts of Asia. In addition to its nutritional value, date fruit has long been known in the traditional medicine to possess health-promoting effects such as its application in gastrointestinal conditions. Ethnopharmacological and historical evidence has indicated that it has been used to treat issues of gastric discomfort, inflammation, and ulcerative disorders. Phytochemical screening of the *Phoenix dactylifera* fruit shows that the fruit contains a wide range of bioactive compounds, such as phenolic acids, flavonoids, carotenoids, tannins, sterols, and dietary fibers[12]. The constituents present in it make it have high antioxidant capacity. Ferulic acid, caffeic acid and flavonoids are phenolic compounds, which are characterized by possessing free-radical scavenging activities and also by their capabilities of regulating oxidative stress pathways. Besides, date fruit is also high in vitamins (vitamin C and some of the B Vitamins), minerals (potassium and magnesium), and natural sugars that can aid in tissue healing and energy production. Experimental research has shown that *P. dactylifera* fruit extracts have an important antioxidant and anti-inflammatory activity in different tissue injury models. These are credited to the increase of the endogenous antioxidant defense, decrease of lipid peroxidation, and suppression of the pro-inflammatory cytokine. These properties are directly applicable to the pathophysiology of ethanol-induced gastric ulceration, in which oxidative stress and inflammation are important mediators of mucosal

injury. Also, date fruit has been found to promote mucosal defense[13][14]. The possible mechanisms are mucus secretion stimulation, maintenance of the production of prostaglandins and maintenance of gastric microcirculation. The protective impact of the content of the fruit fiber can have an additional role too, creating a physical barrier that protects the mucosal field against irritants. Combining all these multifaceted activities may imply that *Phoenix dactylifera* can be used as a cytoprotective entity that can alleviate gastric damage. Notably, being an already popular food, *Phoenix dactylifera* will have a desirable safety profile against synthetic pharmacological treatments. Its extensive usage as a dietary supplement validates the practicality of the translational study to create some functional foods or nutraceutical preparations to be used as gastric protection. Nevertheless, as the experimental evidence on its gastroprotective effect is growing, the results are scattered throughout preclinical research with different methodologies, extract types, dosages, and outcomes measures[15][16]. Hence, a review of the existing preclinical evidence should be done systematically to critically assess the gastroprotective effects of *Phoenix dactylifera* fruit in gastric ulcer models induced by ethanol. An evidence-based evaluation of this kind will help to determine how consistent the effects can be reported, determine underlying mechanisms, evaluate the quality of the methodology, and highlight the gaps in research that should be addressed in the future. This review will achieve a holistic appreciation of the therapeutic promise and mechanism of action of *Phoenix dactylifera* with regard to gastric ulceration by incorporating experimental evidence into a systematic analysis system[17].

MATERIALS AND METHODS

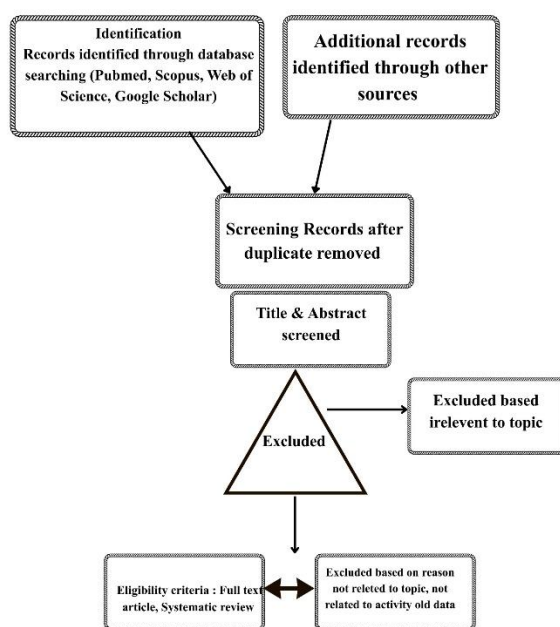
Search strategy



The systematic review was performed based on the guidelines of Preferred Reporting Items of a systematic Review and meta-Analysis (PRISMA 2020). Extensive literature search was conducted to find pertinent preclinical studies on the assessment of the gastroprotective effect of the *Phoenix dactylifera* fruit in ethanol induced gastric ulcer in rats. The database was searched systematically through the electronic databases such as PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar up to the latest available date of the databases. The search strategy was a combination of a search term based on medical subject headings (MeSH) and free-text keywords with Boolean operators (AND

/ OR). The main search words were the following: *Phoenix dactylifera*, date fruit, date palm, gastrointestinal ulcer, ethanol-induced ulcer, gastrointestinal mucosal injury, gastric protection, rat, and experimental ulcer. Each database had its search syntax modified so as to guarantee a thorough search. Besides electronic searches, reference lists of qualified articles and useful review papers were also screened manually in order to find out more studies that could have been overlooked. Only those studies that were in English were taken into consideration. Before screening, duplicate records were eliminated.

Inclusion and exclusion criteria



RESULT

The search of the systematic database identified a total number of records which were identified using electronic databases and screening of the references manually. The same studies were removed before the rest of the studies were screened on the basis of titles and abstracts to determine their relevance. Many articles were filtered at this point because they were deemed

irrelevant to the study of ethanol-induced gastric ulcers models, they did not involve fruits, they were in vitro, or they were review articles. Subsequent eligibility assessment of full-text articles that appeared to be eligible was based on the pre-set screened inclusion and exclusion criteria. At the full-text stage, studies that failed to provide ethanol-specific data, lacked quantitative assessment of ulcers or which used other species



other than rats were filtered out. Finally, a specific number of experimental studies were included in qualitative synthesis meeting all the criteria of eligibility. A PRISMA flow diagram is used to summarize the process of the study selection, which includes identification, screening, eligibility, and inclusion stages.

Characteristics of Included Studies

The included studies were published in various geographical locations, as the world expresses increasing interest in the gastroprotective effect of *Phoenix dactylifera* fruit. They all used rat models, mainly Wistar or Sprague-Dawley strains, whereby animals had average weights of 150-250 g[18][19]. Male rats were used in most experiments to reduce hormonal variation though some have involved both genders. Each group of the experiment usually had up to 5 to 10 animals. Gastric ulceration was induced by ethanol by oral intake of absolute ethanol or high level of ethanol, usually 70-100 percent, after 18-24 hours of fasting. The evaluation of gastric injury was done at the short period after giving ethanol. The intervention entailed the use of *Phoenix dactylifera* fruit extracts to administer the extracts through aqueous, ethanolic or hydroalcoholic extraction procedures. Studies have different dosage levels but most of them are usually in low-to-high dose to test dose- effects. The therapy plans involved pretreatment by a single dose or repeated doses in the short run before the ethanol exposure. The ethanol alone was applied to control groups and usually, the reference groups were compared with other antiulcer standard medicines like omeprazole or ranitidine. Outcome measures were always the ulcer index, the area of the gastric lesion, the percentage of inhibition of ulcer formation, the histopathological evaluation and the biochemical one associated with the oxidative stress and inflammatory situation. In general, the studies found methodological similarity in the

induction of ulcers protocols but differences in the extract preparation and dosing forms[20].

Effects on ulcer index and lesion area

In incorporated studies, application of *Phoenix dactylifera* fruit extracts always led to considerable decrease in ulcer index and gastrointestinal lesion area, as compared to control groups who had been treated with ethanol. The protective effect was often dose-related whereby stronger doses exhibited stronger ulcer inhibition[21][22]. There was variation in percentage inhibition of ulcer formation in studies but usually expressed significant reduction of mucosal injury. Macroscopic analysis indicated the presence of typical hemorrhagic streaks, mucosal erosions and widespread gastric lesions with the administration of ethanol. Pretreatment with *Phoenix dactylifera* extract, on the other hand, significantly ameliorated the severity and magnitude of these lesions. The quantitative index of ulcer values were significantly reduced in treated groups and usually they are characterized by the values like those of standard drug-treated groups. The gastroprotective effect of the fruit extract in a number of studies was comparable with proton pump inhibitors or H₂ receptor antagonists indicating that the fruit extract has potential therapeutic value[23][24]. These findings were further supported by histopathologic examination. Gastric tissues that were exposed to ethanol tissues were usually characterized by epithelial cell exfoliation, submucosal edema, inflammatory infiltrations, and vascular congestions. *Phoenix dactylifera* fruit extract prevented mucosal architecture, inflammatory infiltration and epithelial integrity. All these findings show consistent gastroprotection effects in ethanol induced ulcer models.

Effects on oxidative stress markers



One of the main conclusions of the studies was that *Phoenix dactylifera* fruit extracts modify the parameters of oxidative stress. Gastric injury caused by ethanol was always connected with high malondialdehyde (MDA) concentration, which suggested the increase of lipid peroxidation and oxidative membrane damage[25]. At the same time, antioxidant enzyme activities (such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH)) were also greatly reduced in groups treated with ethanol. Pretreatment of fruit extract of *Phoenix dactylifera* also greatly decreased the level of MDA indicating that it can inhibit lipid peroxidation. At the same time, activities of antioxidant enzymes were brought to the normal levels. The positive changes in the SOD and CAT activities manifested increased superoxide radicals and hydrogen peroxide scavenging, respectively, whereas restoration of the GSH levels was an indication of the improved intracellular redox balance. Such results indicate the fruit extract has strong antioxidant properties that play an important role in its gastroprotective effect[26]. This antioxidant effect can probably be explained by a high level of phenolic and flavonoid compounds in the fruit of *Phoenix dactylifera*, which allows neutralizing free radicals and stabilizing radical oxygen species. The extract alleviates one of the major mechanisms that lead to mucosal damage that occurs in the presence of ethanol by restoring the oxidative balance.

Effects on inflammatory mediators

Besides oxidative stress modification, a number of studies assessed inflammatory outcomes that were related to gastric damage. Exposure to ethanol was reported to elevate pro-inflammatory cytokine tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and expression of cyclooxygenase-2 (COX-2). These are the inflammatory mediators that contribute to the destruction of the mucosal by

facilitating the invasion of neutrophil and vascular permeability as well as edema in the tissues[27]. *Phoenix dactylifera* fruit extract intervention showed a large percentage decrease in these pro-inflammatory markers. Reductions in TNF- α and IL-1 β indicate inhibition of and suppressed inflammatory signalling pathways, whereas regulation of COX-2 expression may aid in recovery of mucosal prostaglandin balance. There were also some studies that indicated decreased myeloperoxidase activity, which showed a decrease in neutrophil infiltration in gastric tissues. These anti-inflammatory actions form an addition to the antioxidant activity of the fruit extract and work together to promote a multi-targeted action of action in countering the ethanol-induced gastric damage[28].

Proposed mechanisms of gastroprotection

According to the evidence that is synthesized, the gastroprotective property of *Phoenix dactylifera* fruit seems to be multifactorial and interconnected. The main mechanism is antioxidant activity, which is the decrease of the lipid peroxidation and increase of endogenous antioxidant defenses. The extract prevents oxidative tissue damage by neutralizing reactive oxygen species to protect cellular membranes. One additional action is a secondary mechanism of the anti-inflammatory modulation via the downregulation of pro-inflammatory cytokines and the suppression of neutrophil entry[29]. Mucosal blood flow preservation and epithelial preservation also have been proposed as contributory factors. Also, other studies show increased mucus secretion and prostaglandins with cytoprotective effects which reinforce the gastric mucosal barrier against ethanol-induced irritation. It is the synergistic effect of the antioxidant, anti-inflammatory and cytoprotective effects, which is likely to explain the strong gastroprotective action in experimental models[30].



Risk of Bias Findings

Methodological quality evaluation based on SYRCLE Risk of Bias tool showed that not all the included studies reported similarly. Most of the studies sufficiently outlined experimental groups and outcome measures, but randomization procedures and allocation concealment were often not reported in detail. The researchers did not consistently mention blinding of investigators and outcome assessors, thereby leaving too much uncertainty in the areas of performance and detection bias. The attrition bias was mostly low because most of the studies had full outcome data. Nevertheless, incomplete methodological transparency could not be excluded in some cases because selective outcome reporting was used. In general, the quality of methodology of involved studies was moderate, which indicates that better reporting standards and compliance with the existing guidelines on animal research are required[31].

DISCUSSION

The current systematic review is a synthesis of the existing preclinical data of the gastroprotective effect of *Phoenix dactylifera* fruit in gastric ulcer models induced by ethanol in rats. The authors have repeatedly shown that fruit-based extracts have a strong ability to reduce gastric mucosal injury as indicated by the decrease in ulcer index, lesion area and histopathological lesions[32][33]. In the literature, the protective properties were often dose-dependent and, in some cases, equal to established antiulcer drugs like proton pump or H₂ receptor blockers. These observations indicate that *Phoenix dactylifera* fruit has more than just nutritional benefits as indicated by their pharmacological activity. One of the key events mediating the observed gastroprotection effect is the regulation of oxidative stress. Gastric injury caused by ethanol is closely linked with

overproduction of reactive oxygen species and loss of endogenous antioxidant protection. The studies that were reviewed had a common finding that the levels of malondialdehyde were reduced and the antioxidant enzymes superoxide dismutase, catalase, and reduced glutathione were restored after the use of *Phoenix dactylifera* extracts. This antioxidant effect can be attributed reasonably to the abundance of phenolic compounds and flavonoids in the fruit which have been known to scavenge free radical and stabilize cell membranes[34][35]. The fruit extract also alleviates a primary causative agent of mucosal injury caused by ethanol by regaining redox balance. Anti-inflammatory modulation is also deemed to play a role in the overall protective profile in addition to antioxidant effects. Inhibition of pro-inflammatory cytokines, tumor necrosis factor-alpha and interleukin-1 beta, and/or inhibition of neutrophil infiltration is an indication that *Phoenix dactylifera* may disrupt inflammatory cascades triggered by ethanol exposure. Mucosal integrity as seen by microscopy also indicates a hypothesis on the role of cytoprotective effect, which can be associated with increased mucus secretion and support of gastric microcirculation. Although the results appear encouraging, there are a number of weaknesses that need to be considered. Heterogeneity is created by variability in extract preparation, dosage regimens and experimental protocols, restricting direct comparison between studies[36][37]. Besides, some flaws in the methodology, especially the insufficient reporting of randomization and blinding, are of concern in terms of possible bias. Notably, the evidence is limited to the acute models of ethanol in rats and care is to be used in translational extrapolation to human gastric ulcer disease[38][39]. Altogether, the existing preclinical evidence indicates the gastroprotective effect of *Phoenix dactylifera* fruit via the multifactorial mechanisms that involve



antioxidant, anti-inflammatory, and cytoprotective activities. Nonetheless, its therapeutic applicability in management of gastric ulcers in man requires standardized experimental models, mechanistic studies on a molecular level and finally well-crafted clinical studies to validate it[40].

FUTURE PROSPECTIVE

The results of the systematic review indicate that *Phoenix dactylifera* fruit has a promising gastroprotective action in gastric ulcer models induced by ethanol, but multiple essential aspects of the research require additional investigation to enhance the evidence base and aid in translational progression[41]. Future studies would focus on standardization of extract preparation, including vivid description of phytochemical profiles, identification of bioactive compounds and quantification of marker compounds[42]. The pharmacological results can be significantly affected by variability in solvent systems, extraction modes, maturation phases and cultivars. Standardizing protocols of extraction and setting quality control parameters will enhance comparability and reproducibility of studies. More sophisticated analytical tools like high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS), and metabolomic profiling need to be combined to determine the major compounds that cause gastroprotective effects[43-45]. Mechanistic studies are also necessary to clarify the mechanisms of action on a molecular basis of the reported antioxidant and anti-inflammatory activities. Although existing evidence emphasizes the need to regulate oxidative stress markers and inflammatory cytokines, future research can investigate intracellular signaling genes including nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-kappa B (NF-kB), mitogen-activated protein kinases (MAPKs), and apoptotic

regulators[46][47]. The analyses of genes (gene expression) and proteins (protein-level analyses) might give more detailed information regarding the cytoprotective mechanisms. Moreover, the possible investigation of nitric oxide pathways, the formation of prostaglandins, and angiogenic factors could help to explain the importance of mucosal blood flow and epithelial regeneration in the mediation of protection. The studies that are available are based on acute ethanol-induced models, which mainly comprise oxidative and chemical damage. Further studies ought to be conducted by incorporating the models of chronic ulcers, such as NSAID-induced and stress-induced ulcer models to dictate whether the protective properties of *Phoenix dactylifera* can be applied beyond acute injury models[48]. Optimization studies in the dose-response are also required in order to determine the effective therapeutic ranges and safety margins. Despite the fruit being used as a dietary constituent in large quantities, and mostly assumed to be safe, systematic toxicological analyses, such as subchronic and chronic toxicity studies, would give greater confidence to its use in treatment. The other significant direction is the pharmacokinetic and bioavailability studies. Active phytoconstituents have not yet been studied in terms of their absorption, distribution, metabolism, and excretion patterns. It is important to know whether these compounds achieve effective concentrations in the gastric mucosa in order to develop a rational formulation[49][50]. The gastrointestinal tract may be better stabilized and act in a targeted manner through encapsulation approaches, nanoformulations, or delivery systems based on functional foods. Finally, a step towards human clinical assessment is a decisive step. Well-conducted pilot clinical trials that determine safety, tolerability and initial efficacy in patients with gastritis or mild gastric ulceration may fill the gap between preclinical results and therapy. These experiments must include accepted



clinical endpoints and biomarker measurements to support mechanistic thoughts based on animal experiments. The introduction of *Phoenix dactylifera* into evidence-based complementary medicine systems has the potential to introduce a new, naturally derived supplement in the management of gastric ulcers.

CONCLUSION

This review systematizes preclinical studies that prove the gastroprotective effect of *Phoenix dactylifera* fruit in ethanol-induced gastric ulcer model in rats. In incorporated literature, extracts based on fruit always decreased ulcer index and lesion size, maintained gastric mucosal structure, and reduced histopathological lesions. Its protective effects were often dose-dependent and in multiple studies similar to standard antiulcer drugs. All these findings imply the presence of high levels of biological activity in *Phoenix dactylifera* fruit besides its nutritional production. The gastroprotective mechanisms seem to be multifactorial in a mechanistic manner. Reestablishing the oxidational balance by lowering the extent of lipid peroxidation and increasing the activity of the endogenous antioxidant enzymes are among the key mechanisms of protection. Synonymous inhibition of pro-inflammatory cytokines and neutrophil infiltration also help in mucosal injury attenuation. Retention of epithelial integrity, possible improvement of mucus secretion, and preservation of microcirculatory activity may also be supportive in the mediation of protection. The coordinated action of antioxidant, anti-inflammatory, and cytoprotective measures contains a logical description of the consistent protective effects in animal experiment models. However, the existing literature is not faultless. Experimental design heterogeneity, extract standardization, and outcome reporting make direct comparisons difficult and prevent

quantitative synthesis. In addition, lack of reporting of all methodological information in some of the studies also presents the possibility of bias. Notably, all the findings are limited to animal models and the generalisation to human gastric ulcer disease needs to be taken with keen interest. To sum up, *Phoenix dactylifera* fruit, because of the combination of antioxidant and anti-inflammatory effects, presents the promising gastroprotective effects against gastric ulcer models induced by ethanol. As these results suggest that it has potential to be used as a natural therapeutic candidate or functional food ingredient to the gastric protection system, more standardized experimental studies and well designed clinical trials should be conducted to confirm its efficacy and safety in human, as well.

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