Sci. Evaluation of Edible Fruits and Spices Used for the Treatment of Peptic Ulcer in Traditional Iranian Medicine

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In traditional Iranian medicine (TIM), several edible fruits and spices are thought to have protective and healing effects on peptic ulcer (PU). The present study was conducted to verify anti-PU activity of these remedies. For this purpose, edible fruits and spices proposed for the management of PU in TIM were collected from TIM sources, and they were searched in modern medical databases to find studies that confirmed their efficacy. Findings from modern investigations support the claims of TIM about the efficacy of many fruits and spices in PU. The fruit of *Phyllanthus emblica* as a beneficial remedy for PU in TIM has been demonstrated to have antioxidant, wound healing, angiogenic, anti-*H. pylori*, cytoprotective, antisecretory, and anti-inflammatory properties. The fruit of *Vitis vinifera* has been found to be anti-*H. pylori*, anti-inflammatory, wound healing, angiogenic, cytoprotective, and antioxidant. The fruit and aril of seed from *Myristica fragrans* exert their beneficial effects in PU by increasing prostaglandin, modulation of nitric oxide and inflammatory mediators, wound healing, antisecretory, antacid, antioxidant, and anti-*H. pylori* activities, and improving angiogenesis. Pharmacological and clinical studies for evaluation of efficacy of all TIM fruits and spices in PU and their possible mechanisms of action are recommended.

1. Introduction

Gastric and duodenal ulcers, entitled as peptic ulcer (PU), are the most prevalent gastrointestinal disorders in the world [1]. PU is a multifactorial and complex disease with unclear etiological factor. It has been demonstrated that PU is a pathological condition in which biological balance between aggressive and defense factors is disturbed. Among aggressive factors, it can be named from gastric acid and pepsin secretion, active free radicals and oxidants, leukotrienes, endothelins, and exogenous factors such as ethanol or non-steroidal anti-inflammatory drugs (NSAIDs). In contrast, gastric mucus, bicarbonate, normal blood flow, prostaglandin (PG), nitric oxide (NO), and antioxidant enzymes such as catalase and glutathione (GSH) work as defense factors [2, 3].

Most of the gastric lesions originate from a chronic infection of gastric mucosa with *Helicobacter pylori* (*H. pylori*). *H. pylori* is a common human pathogen with asymptomatic stomach colonization in nearly 70% of the population and approximately 10%–20% are susceptible for PU [4].

Traditional medicines of all over the world possess different virgin remedies for the treatment of symptomatologies related to many ailments. Thus, they are very important for investigation on their efficacy and phytochemical constituents [5–7]. There are several edible fruits and spices proposed in traditional Iranian medicine (TIM) for the management of PU [8, 9]. Present study conducted to review these fruits and spices and found evidence for their efficacy and biological mechanisms in modern publications. In order to achieve this aim, electronic databases including PubMed,
It showed inhibitory activity on fruit, promoting releasing NO in the intestinal endothelium mucosal morphology [18]. Berberine, as an active constituent and may have a role in improvement of intestinal cytokines [14].

2.2. Berberis vulgaris L.

A glycoside isolated from bitter almond oil healed wounds in rats [13]. Amygdalin, a trivial antacid property [22]. The leaves of C. controversa, C. macrophylla, and C. walteri demonstrated wound healing activity [23].

2.3. Cornus mas L. The fruits showed antioxidant activity [22]. The leaves of C. controversa, C. macrophylla, and C. walteri demonstrated anti- H. pylori activity [23].

2.4. Cucurbita maxima Duch. and C. Pepo L.

Fruit pulp of C. pepo showed protective activity against gastric and duodenal ulcer via enhancing mucosal thickness and increasing alkaline phosphatase enzyme in stomach and duodenum tissue [25]. Triterpenoids from the seeds of C. pepo protected against gastric ulcer via reducing gastric secretion and free and total acidity of gastric juice and its antioxidant activity [24].

2.5. Cydonia vulgaris Pers. syn. C. oblonga Mill. Various components from peel, pulp, and seed of fruit exhibited antioxidant activity [26]. Phenolic compounds from fruits showed gastroprotective properties [27]. Fruit juice and fruit extract demonstrated strong and weak anti-H. pylori activity, respectively [29]. The seed mucilage topically administrated heals toxin-induced skin lesions in rabbits [28].

2.6. Malus domestica Baumg. M. domestica fruit and its isolated phenolic acids demonstrated gastroprotective activity via reducing neutrophil infiltration in gastric tissue and antioxidant activity [30, 31]. The fruit also reduced gastric endothelial cell injury through antioxidant activity [31]. M. domestica peel showed both in vitro and in vivo anti H. pylori activity [32, 33]. Fruit polyphenol revealed gastroprotective activity without significant effect on gastric secretion. It also inhibited lipid peroxidation and production of inflammatory cytokines [34]. However, there is a report on exacerbation of gastric ulcer by fruit polyphenol extract [27].

2.7. Morus alba L. and M. nigra L. Cyanidin-3-O-glucoside, a component isolated from M. alba fruit, showed protective activity against endothelial dysfunction [36]. Ethyl acetate soluble fraction of fruit attenuated gastric ulceration in rat via its antioxidant activity [38]. The leaf had protective activity against gastric ulcer [35] and revealed anti H. pylori as well as antioxidant activity [37].

2.8. Myristica fragrans Houtt. Various investigations have proved strong anti-H. Pylori activity of M. fragrans seed in vitro [39]. Dihydroguaiaretic acid isolated from aril of the seed also demonstrated strong anti H. pylori activity [40]. The seeds suppressed free and total acidity and volume of gastric secretion [42]. The aril of seed showed antioxidant activity in vitro [41]. M. malabarica fruits improved gastric ulcer in mice via increasing PG E2 synthesis, improving angiogenesis, modulating NOS gene expression, producing balance between proinflammatory and anti-inflammatory cytokines, and improving mucin content and antioxidant activity in gastric tissue [44–46]. M. andamanica leaves demonstrated wound healing activity in vivo [47]. A polyherbal formulation containing M. fragrans fruits inhibits gastric ulcer and hypersecretion in rats [43].

2.9. Oryza sativa L. O. sativa bran oil protected gastric mucus from stress-induced ulcers in rats via inhibiting acid secretion. O. sativa reduced basal acid secretion and stimulated gastric acid secretion by histamine in rats [50]. Antioxidant activity of normal and pigmented rice brans and some isolated components has been proved in vitro [48]. O. sativa cooked seeds suppressed intestinal secretion through inhibiting the response of intestinal epithelial crypt cells to adenosine 3',5'-cyclic monophosphate, a major intracellular mediator of secretion [51]. Rice fluid exhibited strong bactericidal activity against H. pylori [49]. In spite of these supportive data, Jayaraj et al. demonstrated that oil derived from rice and rice bran on storage becomes ulcerogenic, while fresh rice bran diet protected mucosa from ulceration [52]. The study evaluating dietary profile of patients with duodenal ulcer showed more ulcer occurrence in patient with rice diets.
Moreover, mucin activity was attenuated, and severity of ulcer induced by pylorus ligation was higher in rice diet rats [53].

2.10. *Phoenix dactylifera* L. Fruit and seed possess antioxidant activity [54, 55]. The fruit ameliorated gastric ulcers via increasing gastric mucin and reducing histamine and gastrin (a gastrointestinal hormone that regulates gastric acid secretion, releases histamine, and regulates gastric endocrine cell proliferation in the plasma) [56].

2.11. *Phyllanthus emblica* L. *P. emblica* fruit purified phenolics demonstrated antioxidant activity *in vitro* [57]. The fruit exhibited wound healing activity via improvement of collagen function and enhancing antioxidant capacity [59]. It protected against gastric ulcer via its antioxidant and cytoprotective activity [60, 62]. Gallic acid enriched extract exhibited healing property on gastric ulcer via increasing PG E$_2$ and proangiogenesis factors, enhancing endothelial NOS (eNOS), and regulation of pro-inflammatory and anti-inflammatory cytokines and antioxidant activity [61, 63]. The fruit ethanol extract demonstrated anti *H. pylori* activity *in vitro* [58].

2.12. *Punica granatum* L. *P. granatum* peel extract protected gastric mucus from gastric ulcer via its antioxidant activity and attenuating gastric acidity [67, 68]. It attenuated acetylcholine-induced contractions and inhibition of the spontaneous movement of the isolated rat ileum [64]. The peel also showed anti *H. pylori* activity [65]. The ointment prepared from the peel extract accelerated wound healing and exhibited antioxidant properties in guinea pigs [66]. The tannins from fruit prevented formation of gastric ulcer, increased NO level and secretion of adherent and free mucus, and exhibited antioxidant activity in gastric mucosa [69].

2.13. *Rhus coriaria* L. The fruit demonstrated antioxidant activity *in vitro* [71, 72]. Ethanol extract of fruit showed antibacterial activity against *H. pylori* [70].

2.14. *Vitis vinifera* L. The seed demonstrated antioxidant activity *in vitro* [73]. The fruit skin and seed revealed anti
Table 2: Pharmacological activities attributed to antipeptic ulcer activity of edible fruits and spices used in TIM for the management of this disease.

| Plant                  | Part/extract                      | Active constituent | Model    | Species | Result                                                                 | Reference |
|------------------------|-----------------------------------|--------------------|----------|---------|----------------------------------------------------------------------|-----------|
| Amygdalus communis     | Powdered fruit                    | —                  | In vitro | —       | Antacid                                                               | [10]      |
|                        | Hull and shell/methanol extract   | —                  | In vitro | —       | Antioxidant                                                           | [11]      |
|                        | Defatted seed/80% acetone extract and its fractions | —                  | In vitro | —       | Antioxidant                                                           | [12]      |
|                        | Nut/oil                           | —                  | Open wound | Rat     | Wound healing |
| Berberis vulgaris      | Fruit/ethanol, methanol and water extract | —                  | In vitro | —       | ↓ NO in intestinal endothelium cell                                   | [15]      |
|                        | —                                 | Berberine          | In vitro | —       | Anti-H. pylori                                                        | [16]      |
|                        | —                                 | Berberine          | In vitro | —       | Improvement of intestinal mucosal morphology |
| Capparis spinosa      | Fruit/water extract               | —                  | —        | Broiler chicken | ↓ GU, ↑ eNOS, and ↓ iNOS mRNA expressions |
| Cornus mas             | Fruit/methanol extract            | —                  | In vitro | —       | Anti-H. pylori                                                        | [22]      |
| Cornus controversa, C. macrophylla, and C. walteri | Leaf/methanol extract | —                  | In vitro | —       | Anti-H. pylori                                                        | [23]      |
| Cucurbita pepo         | Ripe fruit pulp/aqueous extract   | —                  | Aspirin-induced GU and DU | Rat     | ↓ GU and DU, ↑ mucosal thickness, and ↓ alkaline phosphatase enzyme in stomach and duodenum tissue |
|                        | Seed                              | Triterpenoids      | In vitro | —       | Antioxidant                                                          | [24]      |
|                        |                                  |                    |          |         | ↓ GU in all models, ↓ gastric secretion, and ↓ free and total acidity of gastric juice |
| Cydonia vulgaris syn. C. oblonga | Pulp, peel, and seed/methanol extracts | —                  | In vitro | —       | Antioxidant                                                          | [26]      |
|                        | Fruits/phenolic extract           | —                  | In vitro | —       | Antioxidant                                                          | [27]      |
|                        | Seed/mucilagage                   | —                  | Ethanol-induced GU and skin lesions | Rabbit | Healing activity on toxin-induced lesion |
|                        | Fruits juice/70% ethanol extract  | —                  | In vitro | —       | Anti-H. pylori activity                                               | [29]      |
| Malus domestica        | Fruit juice and flavonoids rich extract | —                  | In vitro | —       | Antioxidant                                                          | [30]      |
|                        | Fruit/methanol extract            | Catechin and chlorogenic acid | In vitro | —       | ↓ Gastric endothelial cell injury caused by xanthine-xanthine oxidase and indomethacin, ↑ antioxidant activity, and ↓ lipid peroxidation | [31]      |
| Plant                     | Part/extract                        | Active constituent | Model             | Species            | Result                                                                 | Reference |
|--------------------------|-------------------------------------|--------------------|-------------------|--------------------|----------------------------------------------------------------------|-----------|
| Fruit                    | peel/polyphenol-rich extract        | —                  | In vitro          | —                  | Anti- *H. pylori*, inhibition of *H. pylori*-caused oxidant and free radical production, and bacterial toxin vacuolation and adhesion to tissues | [32]      |
| Fruit/juice and flavonoids extract | —                                 | HCl/ethanol-induced GU | Rat   | GU, ↓ MPO activity in gastric tissue |
| Fruit/methanol extract   | —                                   | Indomethacin-induced PU | Rat   | ↑ P, ↓ lipid peroxidation and oxidative agents in gastric tissue Suppression of *H. pylori*-associated gastritis, inflammation and MDA levels in gastric tissue |
| Peel/polyphenol-rich extract | —                                 | *H. pylori* infection | Mouse | GU in both models, no effect on gastric juice secretion, inhibition of aspirin-induced lipid peroxidation, and ↓ COX2 and HB-EGF mRNA and protein over expression |
| Fruit/polyphenol extract | —                                   | Aspirin-induced and pylorus ligation-induced GU | Rat   | ↓ GU in both models, no effect on gastric juice secretion, inhibition of aspirin-induced lipid peroxidation, and ↓ COX2 and HB-EGF mRNA and protein over expression |
| Fruit/polyphenol extract | —                                   | Ethanol-induced GU | Rat   | ↑ GU |
| Morus alba               | —                                   | Cyanidin-3-O-glucoside | In vitro | —                  | Improvement of endothelial dysfunction                               | [36]      |
| Leaf/water and 80% ethanol extracts | —                                 | —                  | —                 | Anti-*H. pylori*, antioxidant                                      | [37]      |
| Fruit/ethyl acetate soluble fraction | —                                 | —                  | Stress-induced GU | Rat   | ↓ GU, ↓ oxidative stress in tissue                                    | [38]      |
| Leaf/ethanol extract     | —                                   | —                  | Ethanol-induced GU | Rat   | ↓ GU |
| Myristica fragrans       | Seed/methanol extract               | —                  | In vitro          | —                  | Anti-*H. pylori*                                                      | [39]      |
|                         | Aril of seed                        | Dihydroguaiaretic acid | In vitro | —                  | Anti-*H. pylori*                                                      | [40]      |
|                         | Aril of seed/acetone extract and its lignans rich fraction | Lignans | In vitro | —                  | Antioxidant                                                         | [41]      |
| Seed                    | —                                   | Carbachol-induced gastric secretion | Rabbit | ↓ Gastric secretion, ↓ free and total acidity of gastric juice |
| Fruits in a polyherbal formulation | —                                 | Pylorus ligation-induced GU | Rat   | ↓ GU, suppression of gastric hypersecretion |
| Myristica malabarica     | Fruit rind/methanol extract         | —                  | Indomethacin-induced GU | Mouse | ↑ GU healing, ↑ PGE2 synthesis, and ↑ angiogenesis by ↑ pro-angiogenics: VEGF and EGF |
|                         | —                                   | —                  | Indomethacin-induced GU | Mouse | ↑ Ulcer healing, ↑ eNOS and ↓ iNOS expressions, and balance between proinflammatory and anti-inflammatory cytokines | [44]      |

Table 2: Continued.
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| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Fruits rind/methanol extract | Procyanidins                          | Indomethacin-induced GU             | Mouse                     | GU healing, ↑ mucin content, and ↓ lipid peroxidation and ↑ antioxidant activity of gastric tissue | [46]      |

**Myristica andamanica**

| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Leaf/methanol extract        | —                                     | —                                   | Excision wound            | Mouse                    | Wound healing activity                                                 | [47]      |

**Oryza sativa**

| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Bran oil                     | —                                     | Anthocyanins, α-tocopherol, and γ-oryzanol | In vitro                 | —                         | Antioxidant                                                           | [48]      |
| Fluid from unpolished and polished raw rice and popularly cooked Japanese rice | —                                     | —                                   | In vitro                 | —                         | Anti-H. pylori                                                        | [49]      |

**Brachylaena coriacea**

| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Stored rice bran oil, fresh rice bran diet | —                                     | —                                   | Pylorus ligated ulcer     | Rat                      | GU, ↑ stress-induced acid secretion, and ↓ basal and stimulated acid secretion | [50]      |
| Rice diet                    | —                                     | —                                   | Pylorus ligated ulcer     | Rat                      | Ulcer by stored rice bran oil, ↑ ulcer by fresh rice bran diet         | [52]      |

**Phoenix dactylifera**

| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Fruit/methanol-water extract | —                                     | —                                   | In vitro                 | —                         | Antioxidant                                                           | [54]      |
| Seed/oil                     | —                                     | —                                   | In vitro                 | —                         | Antioxidant                                                           | [55]      |
| Fruit and pit/aqueous and ethanol extracts | —                                     | —                                   | Ethanol-induced GU       | Rat                      | Ulcer, ↓ gastric secretion, ↑ mucin activity, and ↑ ulcer severity     | [53]      |

**Phyllanthus emblica**

| Plant                        | Part/extract                          | Active constituent                  | Model                     | Species                  | Result                                                                 | Reference |
|------------------------------|---------------------------------------|-------------------------------------|---------------------------|--------------------------|------------------------------------------------------------------------|-----------|
| Fruit                        | Phenolic compounds                    | In vitro                            | —                         | Antioxidant                                                           | [57]      |
| Fruit/ethanol extract        | —                                     | In vitro                            | —                         | Anti-H. pylori            | Wound healing, collagen function improvement, and ↑ antioxidant enzymes: SOD, GSH, and GPx | [58]      |
| Fruit/ethanol extract        | —                                     | Excision wound                      | Rat                       | ↑ mucus and hexosamine   | GU, ↑ antioxidant activity, and cytoprotective activity: ↑ mucus and hexosamine | [59]      |
| Fruit/polar solvent extract  | —                                     | Indomethacin-GU                     | Rat                       | ↑ GU, ↑ PGE2, and ↑ proangiogenesis factors: VEGF, EGF, von Willebrand Factor VIII, and ↑ eNOS/iNOS ratio | [60]      |
| Fruit/gallic acid enriched ethanol extract | —                                     | Indomethacin-induced GU             | Mouse                     | GU in all models, ↑ intraluminal bleeding, and ↑ GSH of mucus       | [61]      |
| Fruit/juice and methanol extract | —                                     | Ethanol-, indomethacin-, and histamine-induced GU | Rat                       | ↑ GU in all models, ↑ intraluminal bleeding, and ↑ GSH of mucus       | [62]      |
| Plant                        | Part/extract                             | Active constituent | Model                             | Species | Result                                                                 | Reference |
|------------------------------|------------------------------------------|--------------------|------------------------------------|---------|------------------------------------------------------------------------|-----------|
| Gallic acid enriched ethanol extract | Indomethacin-induced GU                  | Mouse              | ↑ GU healing, proinflammatory and anti-inflammatory cytokines regulation, antioxidant activity, and ↓ lipid peroxidation | [63]    |
| Punica granatum              | Fruit peel/aqueous extract               | In vitro           | ↑ Acetylcholine-induced contractions, ↓ spontaneous movement of the isolated rat ileum | [64]    |
| Fruit peel/methanol extract  | In vitro                                 | —                  | Anti- H. pylori                    | [65]    |
| Fruit peel/methanol extract  | Excision wound                           | Guinea pig         | ↑ Wound healing, ↑ collagen, DNA, and tissue proteins | [66]    |
| Fruit peel/aqueous extract   | Ethanol-induced GU                       | Rat                | ↓ GU, ↓ gastric acidity            | [67]    |
| Fruit peel/methanol extract  | Aspirin- and ethanol-induced GU          | Rat                | ↓ GU in both models, ↑ catalase, ↑ GSH, ↑ GPx, ↑ SOD, and ↓ lipid peroxidation | [68]    |
| Fruit                         | Water immersion stress-, pylorus ligation-, and intragastric absolute ethanol-induced ulcer | Rat                | Lipid peroxidation, ↑ NO, ↑ GPx, ↑ SOD in gastric mucosa, and ↑ secretion of adherent mucus and free mucus | [69]    |
| Fruit ethanol extract        | In vitro                                 | —                  | Anti-H. pylori                     | [70]    |
| Rhus coriaria                | Fruit/aqueous extract                    | Gallic acid        | Anti-oxidative activity, ↓ oxidative stress, and ↓ lipid peroxidation in rat isolated hepatocytes | [71]    |
| Fruit/methanol extract       | In vitro                                 | —                  | ↓ lipid peroxidation, Anti-oxidant activity | [72]    |
| Seed/ various extract        | In vitro                                 | —                  | Antioxidant                        | [73]    |
| Fruit skin and seed/ various extract | In vitro                                 | —                  | Anti-H. pylori                     | [74]    |
| Fruit/hydroalcoholic extract | In vitro                                 | —                  | Anti-H. pylori                     | [75]    |
| Fruit juice                  | Resveratrol                              | In vitro           | Anti-H. pylori, ↓ ROS, ↓ inflammatory agents, and improvement of gastric mucosal cell morphological changes induced by H. pylori | [76]    |
| Fruit juice                  | Resveratrol                              | In vitro           | Anti-H. pylori, ↓ ROS, ↓ inflammatory agents, and improvement of gastric mucosal cell morphological changes induced by H. pylori | [77]    |
| Vitis vinifera               | Seed/proanthocyanidin extract            | Resveratrol        | ↑ GU and DU, ↓ lipid peroxidation, and ↓ gastric and duodenal membrane microviscosity | [78]    |
|                              | Acute and chronic water-immersion restraint stress-induced gastric and intestinal oxidative injury | Rat                | ↑ GU, radical scavenging activity, and procyanidins binding ability to stomach surface protein which result in ↑ defense activity of gastric membrane | [79]    |

**Table 2: Continued.**
H. Pylori effects [74, 75]. Proanthocyanidin-rich extract from seed protected against acute and chronic gastric and intestinal oxidative injury through inhibition of lipid peroxidation and membrane microviscosity in gastric and duodenal membrane [78]. It showed higher gastroprotective and antioxidant activity compared to vitamin E and C [80]. The seed also exhibited protective effect against gastric ulcer in rat. Antioxidant activity and strong ability of procyanidins to bind protein covering the stomach surface may be responsible for this protective effect [79]. This protein elevates defense activity of gastric membrane. The seed showed wound healing properties via enhancing angiogenesis and antioxidant activity [81, 83]. Resveratrol, a high abundant polyphenol in red grape fruits, suppressed H. pylori growth, H. pylori-induced interleukin-8 secretion, reactive oxygen species generation, and morphological changes in human gastric epithelial cells [76, 77]. Resveratrol in low dose (2 mg/Kg) demonstrated ulcer healing activity but in high dose (10 mg/Kg) was ulcerogenic. The mechanism of ulcer healing activity in low dose is attributed to inhibition of neutrophil aggregation, stimulation of COX1, PG E2, and eNOS, and improvement of angiogenesis [82].

### 3. Discussion

In TIM, a wide range of medicinal plants have been proposed for the treatment of different gastrointestinal disorders like inflammatory bowel disease, irritable bowel disease, hemorrhoids, and PU [84–87]. In this paper, all of edible fruits and spices claimed to be efficacious in the management of PU were collected from TIM sources, and any scientific evidence that prove their efficacy was retrieved from electronic databases. These remedies have shown their effectiveness on PU via several mechanisms of action including PG enhancement, modulation of inflammatory mediators, and antioxidant, anti H. pylori, wound healing, cytoprotective, and antisecretory activities. Some of the investigated fruits and spices like Myristica fragrans, Phyllanthus emblica, Vitis vinifera, and Punica granatum have shown their beneficial effects in PU by affecting various associated mechanisms. According to published investigations, these fruits and spices seem to be more effective in the management of PU than the other ones. In contrast, for some of these fruits and spices including Morus species, Cornus mas, Rhus cariaaria, and Phoenix dactylifera, just one or two studies on the efficacy and relevant mechanisms have been executed. Advanced scientific studies for evaluation of these herbs on PU and their possible mechanisms are suggested.

Despite many pieces of in vitro and in vivo evidence, no human study was found to confirm the effectiveness of investigated fruits and spices in PU. As shown in Table 1, the plants used in TIM for management of PU are from different families, and there is no exact relationship between the family of plants investigated and their efficacy. No potential side effects have been reported from these remedies. Studies on antiulcer activity of some of investigated fruits and spices have revealed controversial results. For example, stored rice bran oil has shown ulcerogenic activity. Whereas, fresh rice bran diet and rice diet have demonstrated anti-PU properties in animal models [52, 53]. Fruit polyphenol extract of Malus domestica has ulcerogenic effect [27]. In contrast, fruit juice, flavonoids extract, and fruit methanol extract have shown gastroprotective activity in various animal models [30, 31, 34]. Despite different reports on protective activity of berberine, an active compound of Berberis vulgaris, against gastric ulcer [19, 20], there is a report about dose-dependent gastric ulcer inducing activity of this compound [21]. Some of the investigated remedies have shown conflicting results in different doses. Resveratrol, a highly abundant polyphenol in Vitis vinifera fruit, in low dose demonstrated ulcer healing activity but in high dose was ulcerogenic [82].

Overall, there are various edible fruits and spices in TIM for the management of PU which their efficacy had confirmed through various in vitro and in vivo studies. Because of the

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**Table 2: Continued.**

| Plant           | Part/extract | Active constituent | Model                  | Species | Result                                                                 | Reference |
|-----------------|--------------|--------------------|------------------------|---------|----------------------------------------------------------------------|-----------|
| Seed/proanthocyanidin rich extract | —            | —                  | Aspirin- and ethanol-induced GU | Rat     | Ulcer in both models, lipid peroxidation more than Vit E and Vit C; Wound healing, angiogenesis activity and factor: VEGF, and antioxidant function of tissue | [80]      |
| Seed/proanthocyanidin extract | —            | —                  | Excision wound         | Mouse   | 2 mg/Kg: GU healing, MPO, COX1, PGE2, eNOS, and angiogenesis; 10 mg/Kg: ulcerogenic | [82]      |
| —               | —            | —                  | —                      | —       | —                                                                  |           |

\(\text{COX}: \text{cyclooxygenase}; \text{DU}: \text{duodenal ulcer}; \text{EGF}: \text{epidermal growth factor}; \text{eNOS}: \text{endothelial NO synthase}; \text{GPx}: \text{glutathione peroxidase}; \text{GSH}: \text{glutathione}; \text{GU}: \text{gastric ulcer}; \text{H. pylori}: \text{Helicobacter pylori}; \text{HB-EGF}: \text{heparin-binding EGF-like growth factor}; \text{iNOS}: \text{inducible NO synthase}; \text{MDA}: \text{malondialdehyde}; \text{MPO}: \text{myeloperoxidase}; \text{NO}: \text{nitric oxide}; \text{PGE2}: \text{prostaglandin E2}; \text{PU}: \text{peptic ulcer}; \text{ROS}: \text{reactive oxygen species}; \text{SOD}: \text{superoxide dismutase}; \text{TNF-}\alpha: \text{tumor necrosis factor-alpha}; \text{and VEGF}: \text{vascular EGF}.\)
lack of human studies, it is recommended to conduct clinical trials to prove their efficacy and obtain more conclusive results.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| COX          | Cyclooxygenase |
| eNOS         | Endothelial nitric oxide synthase |
| TIM          | Traditional Iranian medicine |
| TNF-α        | Tumor necrosis factor-alpha |

Conflict of Interests

The authors declare that they have no conflict of interests.

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