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ANTIULCEROGENIC BENEFITS OF HERBAL INGREDIENTS IN ETHANOL-INDUCED ANIMAL MODELS

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Abstract

Background: Gastric ulcer is a common disorder in digestive system. Alcohol consumption is one of the key risk factor in the pathogenesis of gastric ulcer. Although therapeutic approaches are widely available, preventive regimens are limited. Numerous studies have demonstrated that herbal medicines display preventive benefit in the development of ethanol-induced gastric ulcers in both rat and mouse models. The preventive efficacy of herbal medicines on the development of ethanol-induced gastric ulcers is comparable or superior to histamine receptor 2 antagonists. But herbal medicines have fewer side effects.
Materials and Methods: Keywords including gastric ulcer, herbal medicines, prevention and natural ingredients were used to search on http://www.ncbi.nlm.nih.gov/pubmed. The search was performed on January 12, 2014. Only articles published in English were used in this review.
Result and Conclusion: According to the mechanisms of their action and pathogenesis of gastric ulcer, combination of certain herbal medicines could be a valuable alternative to prevent the development of gastric ulcer, particularly for the subjects who are at a higher risk of developing gastric ulcer.

Key words: Herbal Medicines, Gastric ulcer, Prevention, Animal models, Alcohol

Introduction

Among the diseases of upper digestive tract, gastric ulcer is the most common disorder. The prevalence of gastric ulcer is 2.0% in Western populations (Akdamar et al., 1986; Aro et al., 2006; Bernersen et al., 1990) and annual incidence rates range 0.10-0.19% (Groenen et al., 2009). In Taiwan and mainland China, the prevalences of gastric ulcer are 4.7% and 6.1%, respectively (Li et al., 2010; Wang et al., 2011). Over 22% of dyspeptic patients had gastric ulcer (Wong et al., 1998). 0.337 $^{0}/_{00}$ of general population was hospitalized due to gastric ulcer from 1998 to 2005 in USA (Feinstein et al., 2010) and in 1988, the mortality rate of gastric ulcer was 0.19% in USA (Hillman and Bloom, 1989). Gastric ulcer is not only associated with gastric cancer (Hansson et al., 1996; Molloy and Sonnenberg, 1997), but also has significant negative impact on the quality of patients' life, the work productivity and medical burden (Barkun and Leontiadis, 2010; Sonnenberg and Everhart, 1997; Taniyama et al., 2011). For example, in Russia, over 98% of patients with gastric ulcer experienced abdominal pain (Grebenev and Sheptulin, 1992). In USA, the annual expenditures attributed to recent ulcers amounted to $5.65 billion (Taniyama et al., 2011) while in Japan, it was estimated that the 5-year medical cost per patient ranged ¥169,719 to ¥390,921, depending on the type of medicines employed in 2001(Ikeda et al., 2001). In 2011, total 9-month medical cost per patient ranged ¥237,467 to ¥447,377 (Taniyama et al., 2011).

Gastric ulcer often occurs in people who smoke or use nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol consumption (Bujanda 2000; García Rodríguez and Hernández-Díaz, 2004; Ko and Cho, 2000; Maity et al., 2003). Although several non-surgical approaches, including proton-pump inhibitors, antibacterial agents and histamine 2 receptor antagonists, are available to effectively treat gastric ulcer (Bago et al., 2004; Gloria et al., 1989; Ikeda et al., 2001), the preventive regimen is still limited. Some studies showed that over 90% of patients with peptic ulcers were related to Helicobacter pylori (H. pylori) infection (Arroyo et al., 2004; Chen et al., 2010) and H. pylori eradication could effectively treat and prevent gastric ulcer (Arkkila et al., 2005; Chan et al., 2002; You et al., 2006). But recent study indicates that only10% of patients with gastric ulcer are H. pylori positive (McJunkin et al., 2011). Moreover, a clinical study demonstrated that H. pylori eradication did not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment (de Leest et al., 2007). In addition, a meta-analysis showed that H. pylori eradication was not as effective as proton pump inhibitors for preventing NSAIDs-associated ulcers (Vergara et al., 2005). Even though proton pump inhibitors, H2 blockers and prostaglandin E1 analog display some preventive benefit for gastric ulcer (Cullen et al., 1998; Graham et al., 2002; Hawkey et al., 1998; Lee et al., 2014; Medlock et al., 2013; Raskin et al., 1995 and 1996; Scheiman et al., 2006), an over 77% adverse effect rate could prevent these drugs from clinical usage (Lee et al., 2014; Raskin et al., 1996). In contrast, studies have demonstrated that herbal medicines can effectively prevent the formation of gastric ulcer with fewer side effects in various animal models, suggesting the potential utilization of herbal medicines for preventing gastric and/or duodenal ulcers. Because ethanol is one of the major risk factors associated with gastric ulcer, and a substantial portion of peoples (about 0.5 billion) drink alcohol (http://hb.sina.com.cn/health/ysbj/2013-01-20/08193398.html), particularly in the northern China, in this review, we focus on the antiulcerogenic effects of herbal remedies and the mechanisms of their action in the animal model of ethanol-induced gastric ulcer. Due to the complexity of mechanisms and safety of herbal mixtures, only the influences of single herbal ingredient on gastric ulcer are reviewed in this paper.

Efficacy

Ethanol-induced ulcer in rats is a common animal model for gastric ulcer research. Studies have shown that a number of herbal ingredients exhibit the preventive benefits in the development of ethanol-induced gastric ulcer in murine model (Table 1). Huang, et al. (2013), showed that pre-fed rats with ginseng extract at the dose range of 250 – 1250 mg/kg body weight for 28 days induced a dose-dependent anti-ulcerogenic benefit (Golbabapour et al., 2013). Moreover, pre-fed rats with aqueous extract of Sukari date fruit for 14 days significantly reduced the incidence and the severity of gastric ulcer-induced by ethanol (Al-Qarawi et al., 2005). Similarly, rats pre-fed with *Morus alba* extract for 4 days displayed significant low ulcer index, with a protective efficacy comparable to lansoprazole, in an ethanol-induced ulcer model (Ahmad et al., 2013). Not only long term administrations of herbal ingredient prevent the development of gastric ulcer, short term application of herbal extract also exhibits antiulcerogenic benefit. Abdelwahab, et al. (2011) reported that pre-fed rats with methanolic extract of *Boesenbergia rotunda* one hour prior induction of gastric ulcer induced a dose-dependent reduction in ulcer index in addition to elevation in gastric pH and mucus content. 2 hours prior to ulcer induction, oral administration of 20% aqueous extract of *Laurus nobilis* seeds almost completely protected stomach damage induced by absolute ethanol (0.5ml/100g body weight) (Afifi et al., 1997). Interestingly, co-administrations of herbal ingredient and ethanol also prevent the development of ethanol-induced gastric ulcer. For instance, co-administrations of ethanol and achyranthes aspera Linn leaf extract at a dose of 600mg/KG body weight for 7 days caused a 36% inhibition of ulcerogenesis (Das et al., 2012). Besides oral administration, either IP or subcutaneous injection of herbal extract also displays antiulcerogenic benefit (Baggio et al., 2007; Gürbüz and Yesilada, 2007). The efficacy of antiulcerogenic effect of herbal ingredient is comparable or superior to conventional agents. For example, the antiulcerogenic efficacy of *Boesenbergia rotunda* at the dose of 400mg/kg was superior to omeprazole (20 mg/kg), a proton pump inhibitor used in the treatment of gastric ulcer (Abdelwahab et al., 2011). In addition, methanolic extract of pomegranate induced the inhibitory effect similar to ranitidine, a histamine H2-receptor antagonist, in ethanol-induced ulcer model (Ajaikumar et al., 2005). Likewise, pretreatment of rats with *Corchorus olitorius* leaf extract (400mg/kg body weight) normalized gastric pH and induced 100% inhibition of ulcer formation while omeprazole only induced 80% inhibition in ethanol-induced gastric ulcer (Al Batran et al., 2013). Similarly, the inhibitory effect of beeswax extract at a dose of 25mg/kg body weight was superior to the same dose of cimetidine in ethanol-induced gastric ulcer (Carbajal et al., 1995). These evidences indicate that either repeated or single administration of herbal ingredient can prevent the development of gastric ulcer induced by ethanol.

In general, the antiulcerogenic efficacy of herbal ingredients is dose dependent, i.e., the higher dose, the higher efficacy. But some herbal ingredients display a lower protective efficacy at a higher dose than that at lower dose. For example, 50 mg/kg guarana seed extract caused 56% inhibition of gastric ulcer while 100 mg/kg induced 37% inhibition (Campos et al., 2003). Consistently, 50 mg/kg *anacardium humile St. Hil* leaf extract induced 66% inhibition while 200 mg/kg only induced 9% inhibition of ulcerogenesis (Luiz-Ferreira et al., 2010). These could reflect, in part, adverse effect induced by a higher dose of herbal ingredient.

It is worthwhile to note that the methods of herbal preparation can affect the efficacy of certain herbal medicines. For instance, orally given aqueous extract of date fruit induced a 40% inhibition of ulcer index while ethanol extract caused a 55% inhibition in ethanol-induced gastric ulcer (Al-Qarawi et al., 2005). Likewise, 125mg of euphorbia cuneata Vahl.-extracted with chloroform or ethanol only induced a 30% inhibition while the same dose of ethyl acetate extract induced 58% inhibition in ulcerogenesis in an ethanol-induced gastric ulcer model (Awaad et al., 2013). Melanchauski et al. (2013) reported that 100mg/kg of the methanolic extract of Ailanthus excels bark caused 56% inhibition of ulcerogenesis while the same dose of diethyl ether extract induced 83% inhibition, which was the same efficacy as conventional antiulcer agent, such as carbenoxolone. 15 min prior to induction of gastric ulcer, orally given olive oil extract of Momordica charantia L. at a dose of 330 mg/kg lowered ulcer index by 95% while ethanol extract a dose of 310 mg/kg only induced a 56% reduction in ulcer index (Gürbüz et al., 2000). But 100 mg/kg of its methanolic extract caused a 61% reduction in ulcer index (Alam et al., 2009). Moreover, hexane extracts of Combretum duarteanum Cambess leaf and *Dodonaea viscosa* were more effective than their ethanolic or water extract (Al-Howiriny et al., 2005; de Morais Lima et al., 2013). Therefore, to maximize the efficacy of each herbal ingredient, an appropriate extract method should be employed.

Safety

Herbal medicines and their extracts are generally safe. In the acute toxicity studies, the animals orally given the *Cardiospermum halicacabum* Linnextract (4 and 6 g/kg) did not manifest any significant clinical or macroscopical toxic signs over 2-week period. In short term toxicity studies, the herbal extract treatment (400 and 800 mg/kg (p.o.) for 14 days) did not cause mortality of rats (Sheeba and Asha, 2006). No death or significant toxicity was observed in animals treated with *Parkia speciosa* leaf extract at doses of 1, 3 or 5 g/kg for 14 days, as evaluated based on clinical and histopathological observations (Al Batran et al., 2013). Similarly, the extract of *Laurus nobilis* seeds at a dose of 200mg/kg body weight could effectively prevent the development of gastric ulcer induced by ethanol while the LD50 for *Laurus nobilis* seed extract was 13.66 g/kg body weight in male albino mice (Afifi et al., 1997). Likewise, a single oral administration of methanolic extract of *Mouriri pusa* at a dose of 500 mg/kg exhibited a potent antiulcerogenic activity in an ethanol-induced ulcer model. However, a single oral administration of the methanolic extract of *Mouriri pusa* up to a dose of 5000 mg/kg did not produce any signs or symptoms of acute toxicity in the treated animals. During 14 days after the administration of methanolic extract, no animal died, and no significant changes in daily body or organ weight were observed by the end of the study. At autopsy, no significant changes or lesions were observed in the internal organs of each animal (Al Mofleh et al., 2007). In particular, some of the herbal ingredients such as data, strawberry, cashew and bitter melon that exhibit antiulcerogenic benefit are edible. Hence, herbal ingredients are safe for clinical usage.

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Table 1: Herbal Medicines That Prevent the Development of Ethanol–Induced Gastric Ulcer

Herbal Ingredients	Species	Pretreatment Time	References
1. *Boesenbergia rotunda* (L.) Mansf.	Rat	1 hr	Abdelwahab et al. (2011)
2. *Morus alba* L	Rat	4 days	Ahmad et al. (2013)
3. Guarana seed (*Paullinia cupana* Mart.)	Rat	1 hr	Campos et al. (2003)
4. Seeds of *Laurus nobilis*	Rat	15 min	Afifi et al. (1997); Gürbüz et al. (2002)
5. *Asphodelus aestivus* (*A. microcarpus. A. ramosus.)*	Rat	15 min	Gürbüz et al. (2002)
6. *Cichorium intybus*	Rat	15 min	Gürbüz et al. (2002)
7. *Equisetum palustre*	Rat	15 min	Gürbüz et al. (2002)
8. *Viscum album* ssp. album	Rat	15 min	Gürbüz et al. (2002)
9. *Malva neglecta*	Rat	15 min	Gürbüz et al. (2005)
10. *Potentilla reptans*	Rat	15 min	Gürbüz et al. (2005)
11. *Rumex patientia*	Rat	15 min	Gürbüz et al. (2005)
12. *Sanguisorba minor ssp*. muricata(*Poterium sanguisorba*)	Rat	15 min	Gürbüz et al. (2005)
13. *Sideritis caesarea(Dagcayi)*	Rat	15 min	Gürbüz et al. (2005)
14. *Verbascum cheiranthifolium var*. cheiranthifolium(*Calba, yalangi)*	Rat	15 min	Gürbüz et al. (2005)
15. Phoenix dactylifera L.	Rat	14 days	Al-Qarawi et al. (2005)
16. *Cardiospermum halicacabum* Linn. (Sapindaceae)	Rat	30 min	Sheeba and Asha (2006)
17. *Punica granatum* L.	Rat	1 hr	Ajaikumar et al. (2005)
18. *Achyranthes aspera* Linn.	Rat	7 days[1]	Das et al. (2012)
19. Leaves of *Corchorus olitorius*	Rat	1 hr	Al Batran et al. (2013)
20. Beeswax	Rat	1 hr	Carbajal et al. (1995)
21. Leaves of *Parkia speciosa*	Rat	1 hr	Al Batran et al. (2013)
22. Flowers of *Opuntia ficus* indica *F. inermis*	Rat	1 hr	Alimi et al. (2011)
23. Bark of *Rhus tripartitum* root	Rat	1 hr	Alimi et al. (2013)
24. *Gymnema sylvestre*	Rat	1 hr	Al-Rejaie et al. (2012)
25. Strawberry	Rat	10 days	Alvarez-Suarez et al. (2011)
26. Bark of *Samanea saman* (Jacq) Merr	Rat	1 hr	Arumugam et al. (2011)
27. *Euphorbia cuneata* Vahl	Rat	1 day	Awaad et al. (2013)
28. *Ginkgo biloba*	Rat	30 min IV	Chen et al. (2005)
29. *Nigella sativa* oil	Rat	14 days	El-Dakhakhny et al. (2000); Kanter et al. (2005)
30. Leaves of *M. pruriens*	Rat	1 hr	Golbabapour et al. (2013)
31. Leaves and root of Ginseng	Rat	1 hr or 28 days	Huang et al. (2013); Sun et al. 1991 and 1992); Yeo et al. (2008)
32. *Ailanthus excels* bark（Abies excelsa）	Rat	1 hr	Melanchauski et al. (2010)
33. Sesame oil	Rat	1 hr	Hsu et al. (2009)
34. Bark of *Entandrophragma utile*	Rat	2 hr	John and Onabanjo (1990)
35. Garlic oil	Rat	30 min	Khosla et al. (2004)
36. *Foeniculum vulgare*	Rat	1 hr	Birdane et al. (2007)
37. Leaves of *Moringa oleifera* (Lam)	mouse	5 days	Verma et al. (2012)
38. Root of *Moringa oleifera*	Rat	1 hr	Patel Ankur et al. (2012)
39. Leaves of *Bauhinia purpurea* L.	Rat	30 min	Hisam et al. (2012)；Zakaria et al. (2012)
40. *Maytenus ilicifolia* Mart. ex. Reiss	Rat	30 min, IP	Baggio et al. (2007)
41. Naringenin	Rat	4 hr	Motilva et al. (1994)
42. *Nigella sativa*	Rat	1 hr	Kanter et al. (2006)
43. Propolis	Rat	30 min or 1 hr	de Barros et al. (2007); Liu et al. (2002)
44. Rutin	Rat	1 hr	Pérez Guerrero et al. (1994)
45. *Gynura procumbens*Leaves*Gynura procumbens*	Rat	1 hr	Mahmood et al. (2010)
46. chelerythrine	Mouse	4 days	Li et al. (2014)
47. *Terminalia belerica* Roxb.	Mouse	1 hr	Jawanjal et al. (2012)
48. *Pithecellobium dulce*	Rat	30 days	Megala and Geetha(2012)
49. *Momordica dioica* roxb.	Rat	5 days	Vijayakumar et al. (2011)
50. *Momordica charantia* L.	Rat	15 min or 1 hr	Alam et al. (2009); Gürbüz et al. (2010)
51. *Syngonanthus arthrotrichus* SILVEIRA (sempre-vivas mini-saia,)	Rat	30 min	Batista et al. (2004)

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52. *Pimpinella anisum* L	Rat	30 min	Al Mofleh et al. (2007)
53. Leaves of *Alchornea triplinervia* (*Alchornea janeirensis* Casar.)	Rat	1 hr	Lima et al. (2008)
54. Leaves of *Eugenia jambolana*	Rat	10 days	Chaturvedi et al. (2007)
55. Essential oil of *Croton zehntneri* (canela de cunhaˆ)	Mouse	1 hr	Coelho-de-Souza et al. (2013)
56. *Mouriri pusa* Gardn.(*Melastomaceae.* Silverwood)	Rat	1 hr	Andreo et al. (2006)
57. Aerial parts of *Cissus sicyoides*	Rat	30 min	de Paula Ferreira et al. (2008)
58. *Maytenus robusta* leaf	Rat	1 hr	de Andrade et al. (2007)
59. leaves of *Combretum duarteanum* Cambess	Rat	1 hr	de Morais Lima et al. (2013)
60. *Commiphora opobalsamum* (L.) Engl.	Rat	30 min	Al-Howiriny et al. (2005)
61. *Petroselinum crispum*. (Petroselinum Hill, Parsley)	Rat	30 min	Al-Howiriny et al. (2003)
62. *Emblica officinalis* Gaertn(*Phyllanthus Emblica,* Amlaj**)**	Rat	30 min	Al-Rehaily et al. (2002)
63. leaves of *Argyreia speciosa*	Rat	5 days	Jaiswal et al. (2011)
64. *Dodonaea viscosa* Linn.	Rat	30 min	Arun and Asha (2008)
65. *Cistus incanus* L.	Rat	10 min	Attaguile et al. (1995)
66. Flowers of *Baccharis illinita* DC (Cha-ventura, Erva milagrosa)	Rat	1 hr	Baggio et al. (2003)
67. Aerial parts of *Mikania laevigata* Schultz Bip.(guaco-do-mato)	Rat	30 min	Bighetti et al. (2005)
68. Leaves of *Amaranthus tricolor* Linn.	Rat	1 hr	Devaraj and Krishna(2011)
69. Bark of *Terminalia arjuna*	Rat	7 days	Devi et al. (2007)
70. leaves of *Ocimum sanctum* Linn. (*Ocimum tenuiflorum*)	Rat	5 days	Dharmani et al. (2004); Goel et al. (2005)
71. leaves of *Allophylus serratus* (Perakudikkai, Siruvalli)	Rat	45 min	Dharmani et al. (2005)
72. Aerial parts of *Artemisia annua* L.	Rat	1 hr	Dias et al. (2001)
73. Aerial parts of *Hyptis crenata* Pohl ex Benth (hortelã-brava, hortelã do campo)	Mouse	45 min	Diniz et al. (2013)
74. Bacopa monniera	Rat	5 days	Sairam et al. (2001)
75. Bupleurum falcatum L.	Rat	50 min	Sun et al. (1991)
76. Essential oil of *Carlina acanthifolia* root	Rat	60 min	Dordević et al. (2007)
77. Root of *Arctium lappa* L.（Bardana）	Rat	60 min	Dos Santos et al. (2008)
78. *Veronicastrum axillare*	Rat	14 days	Du et al. (2013)
79. *Pithecellobium jiringa* (*Archidendron jiringa, Pithecellobium lobatum*）	Rat	1 hr	Ibrahim et al. (2012)
80. Purple corn husks	Rat	unspecified	Li et al. (2008)
81. Cashew nut-shell (*Anacardium occidentale*)	Mouse	45 min	Morais et al. (2010)
82. *Artemisia asiatica*	Rat	1 hr	Park et al. (2008)
83. leaves of *Plectranthus grandis*	Mouse	1 hr	Rodrigues Pde et al. (2010)
84. leaves of Byrsonima sericea (murici. leaf)	Mouse	1 hr	Rodrigues PA et al. (2012)
85. Bark of *Mitrella kentii* (Blume) Miq. (Fissistigma mabiformis (Griff.) Merr., or *Melodorum clavipes* Hance)	Rat	1 hr	Sidahmed et al. (2013)
86. Root of *Cyclea peltata* (Lam.) Hook. f. & Thoms. (Menispermaceae, Padathaali or Padakizhangu)	Mouse	30 min	Shine et al. (2009)
87. Flowers of *Spartium junceum*	Rat	1 hr	Yeşilada et al. (2000)
88. leaves of *Anacardium humile* St. Hil (cajuzinho do cerrado)	Rat	1 hr	Luiz-Ferreira et al. (2010)
89. leaves of *Parkia platycephala* Benth. (visgueira, or fava bean tree or fava-de-bolota)	Mouse	1 hr	Fernandes et al. (2010)
90.*Careya arborea* Roxb.Leaves	Rat	5 days	Gupta and Rao(2014)
91. *Decalepis hamiltonii* Wight & Arn root (Swallow root)	Rat	14 days	Srikanta et al. (2007)
92. leaves of *Cinnamomum tamala* T. Nees & Eber	Rat	5 days	Eswaran et al. (2010)
93. Seeds of *Garcinia kola* Heckel (bitter kola)	Rat	45 min	Onasanwo et al. (2011)
94. Fruitof *Ficus glomerata* Roxb	Rat	5 days	Rao et al. (2008)
95. *Tabebuia avellanedae* bark	Rat	1 hr	Twardowschy et al. (2008)
96. leaves of *Tectona grandis*	Rat	45 min	Singh et al. (2010)
97. *Angelica polymorpha* Maxim	Mouse	3 days	Wang et al. (2009)
98. Bark of *Zanthoxylum rhoifolium* Lam. (mamica de cadela)	Mouse	1 hr	Freitas et al. (2011)
99. Stem bark of *Quassia amara* L. (Amargo)	Rat	7 days	García-Barrantes and Badilla(2011)
100. Stem bark of *Pteleopsis suberosa* Engl. et Diels. (terenifù)	Rat	1 hr	Germanò et al. (2008)
101. Stem bark of *Anogeissus latifolia*	Rat	5 days	Govindarajan et al. (2006)
102. *Annona squamosa* twigs (*sugar apple*)	Rat	45 min	Yadav et al. (2011)

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103. Aerial parts of *Cleome viscosa* Linn.	Rat	5 days	Gupta et al. (2013)
104. Aerial parts of *Eqiusetum palustre* L.	Rat	1 hr	Gurbuz et al. (2009)
105. Flowers of *Centaurea solstitialis* L. ssp. Solstitialis	Mouse	30 min (subcutaneous injection)	Gürbüz et al. (2007)
106. Green tea	Rat	1 hr	Hamaishi et al. (2006)
107. Root of Hedranthera barteri	Rat	45 min	Onasanwo et al. (2010)
108. leaves of *Senecio candicans DC* (*Callichilia barteri* (Hook.f.) Stapf.)	Rat	30 min	Hariprasath et al. (2012)
109. leaves of *Baccharis genistelloides Pers. (Quimsa-kuchu)*	Rat	30 min	Gonzales et al. (2010)
110. Leaves of *Baccharis rubricaulis Rusby. (Chillca)*	Rat	30 min	Gonzales et al. (2010)
111. leaves of *Phoradendron* crassifolium *Eichl.(Solda solda)*	Rat	30 min	Gonzales et al. (2010)
112. leaves of *Franseria artemisioides Willd. (Markju)*	Rat	30 min	Gonzales et al. (2010)
113. leaves of *Rumex obtusifolius L.* (Kento*)*	Rat	30 min	Gonzales et al. (2010)
114. leaves of *Plantago australis Lam.* (Kara llanten)	Rat	30 min	Gonzales et al. (2010)
115. Leaves of *Satureja boliviana* Briq. (Khoa)	Rat	30 min	Gonzales et al. (2010)
116. Bark of *Aparisthmium cordatum* (*ariquena queimosa*)	Rat	1 hr	Hiruma-Lima et al. (2001)
117. Seeds of *Anethum graveolens* L.	Mouse	30 min	Hosseinzadeh et al. (2002)
118. ArtichokeLeaves	Rat	2 hr	Ishida et al. (2010)
119. Fruit of *Amomum subulatum* Roxb, (cardamom , kalan or Bari Ilaichi)	Rat	30 min	Jafri et al. (2001); Jamal et al. (2006)
120. Fruit of *Solanum nigrum Linn.* (Black nightshade*)*	Rat	3 days	Jainu and Devi(2006)
121. leaves of *Croton campestris* A. St.-Hill	Mouse	30 min	Júnior et al. (2013)
122. *Haematococcus pluvialis*	Rat	21 days	Kamath et al. (2008)
123.Leaves of *Portulaca oleracea* L.	Mouse	30 min	Karimi et al. (2004)
124. Bark of *Pradosia huberi* (*casca-doce or pau-doce)*	Mouse	1 hr	Kushima et al. (2005)
125.Leaves of *Davilla elliptica* 126.Leaves of *Davilla nitida* (sambaibinha or cipó-de-fogo)	Mouse	1 hr	Kushima et al. (2009)
127. Fruit of *Xylocarpus granatum* (pussur)	Rat	45 min	Lakshmi et al. (2010)
128. Root of *Potentilla fulgens* (Wall.) ex Hook. (Himalayan Cinquefoil or Bajradanti)	Rat	7 days	Laloo et al. (2013)
129. *Polygala paniculata* L. (arba-de-são-joão, bromil, vassourinha branca or mimosa)	Rat	1hr	Lapa Fda et al. (2007)
130. Seeds of *Rosa canina* L.	Rat	30 min	Lattanzio et al. (2011)
131. Aerial parts of *Piper aleyreanum* C. DC (Jo ~ao brandinho,pimentalonga)	Rat	1hr	Lima et al. (2012)
132.Leavesof *Byrsonima fagifolia* Nied	Rat	1hr	Lima et al. (2008)
133.Leavesof *Psidium guajava* Linn (guajava)	Rat	3 days	Livingston Raja and Sundar(2012)
134. Black tea	Rat	7 days	Maity et al. (1998)
135. Seeds of Securigera securidaca L.	Rat	1hr	Mard et al. (2008)
136. Stem bark of *Stryphnodendron adstringens* (Mart.) coville (barbatimao)	Rat	1hr	Martins et al. (2002)
137. Black chokeberry fruit	Rat	30 min	Matsumoto et al. (2004)
138. Bark of *Qualea parviflora* Mart.	Mouse	1hr	Mazzolin et al. (2010)
139. *Scoparia dulcis* Linn.(*vassourinha*)	Rat	1hr	Mesía-Vela et al. (2007)
140. *Terminalia chebula* fruit (ink tree or chebulic myrobalan fruit)	Rat	45 min	Mishra et al. (2013)
141.Leavesof *Mouriri elliptica(*coroa-de-frade or coroa*)*	Mouse	1hr	Moleiro et al. (2009)
142. Root of *Cassia sieberiana* (*Cassia kotschyana Oliv*.)	Rat	7 days	Nartey et al. (2012a,b)
143.Leavesof *Gongronema latifolium*	Diabetic Rat	14 days	Owu et al. (2012)
144.Leavesof *Achillea millefolium L.*	Rat	1hr	Potrich et al. (2010)
145. *Benincasa hispida* (Thunb.) Cogn. Fruit (*Bhuru Kolu* or *Safed Kolu*)	Rat	1hr	Rachchh and Jain(2008)
146. *Utleria salicifolia* rhizome (Mahali kizhangu)	Rat	5 days	Rao et al. (2004)
147. Stem barks and fruits of *Hymenaea stigonocarpa* Mart. ex Hayne (jatobá-do-cerrado)	Rat	1hr	Rodrigues et al. (2012)
148.Leavesof *Cordia verbenacea* DC (erva baleeira)	Mouse	1hr	Roldão et al. (2008)
149. Citrus lemon	Rat	1hr	Rozza et al. (2011)
150. *Centella asiatica* Linn (Rasayana in Ayurveda)	Rat	5 days	Sairam et al. (2001)
151. Inflorescences of *Achyrocline satureoides*(Lam.) DC (Marcela or	Rat	1hr	Santin et al. (2010)

Macela)			
152. Mango leaves	Mouse	50 min	Severi et al. (2009)
153. Stem bark of *Manilkara hexandra* (Roxb.) Dubard (*Mimusops hexandra Roxb*).	Rat	1hr	Shah et al. (2004)
154. Bark of *Mimusops elengi* L.(Bakul, aulsari)	Rat	1hr	Shah et al. (2003)
155. Root of *Calotropis procera*	Rat	30 min	Sen et al. (1998)
156. Root of *Pluchea indica* Less.	Rat	1hr	Sen et al. (1993)
157. Seeds of *Ocimum basilicum* Linn (Kali Tulsi)	Rat	30 min(IP)	Singh et al. (1999)
158. *Peganum harmala* seeds (harmal)	Rat	45 min	Singh et al. (2013)
159.Leavesand root of *Flabellaria paniculata*	Rat	1hr	Sofidiya et al. (2012)
160. *Voacanga Africana* fruit	Rat	1hr	Tan and Nyasse(2000)
161. Aerial parts of *Tanacetum vulgare*	Rat	30 min	Tournier et al. (1999)
162. *Artemisia douglasiana* Bess	Rat	1hr	Repetto et al. (2003)
163. Fruit of *Emblica officinalis*	Rat	5 days	Sairam et al. (2002)
164. Bark of *Cratoxylum arborescens*(Vahl) Blume	Rat	1hr	Sidahmed et al. (2013)
165.Leaves of *Jasminum grandiflorum* L.	Rat	30 min	Umamaheswari et al. (2007)
166. Root of *Aerva persica* （*Celosia lanata* L）	Rat	45 min	Vasudeva et al. (2012)
167. Leaves of *Cenostigma macrophyllum* Tul. var. acuminata Teles Freire (caneleiro or canela-de-velho)	Rat	1hr	Viana et al. (2013)
168.Leavesof *Andrographis paniculata* (*hempedu bumi*)	Rat	1hr	Wasman et al. (2011)

[1]7 days with ethanol and herbal extract; IP: Intraperitoneal; IV: Intravenous;

Table 2: The Efficacy and Safety of Herbal Medicines That Prevent the Development of Ethanol –induced Gastric Ulcer

Herbal Ingredient No. (Refer to Table 1)	Efficacy				Adverse Effects
	Herbal Ingredient		Positive Control		
	Dose (mg/kg body weight)	Inhibition (%)	Agent & Dose (mg/kg body weight)	Inhibition (%)	
No. 1	50 - 400	51- 95	Omeprazole 20	77	No adverse effects were observed at a single dose of 5g/kg body weight
No. 2	2.5 - 10	26 - 58	Lansoprazole 30	67	No adverse effects were observed at a dose of 10mg/kg body weight
No. 3	50 - 100	56 - 37	N/D		N/D
No. 4	350	84			
No. 5	1280	95			
No. 6	3280	97		100	LD50=13.36g/kg [43]
No. 7	1350	95			
No. 8	1120	91			
No. 9	1243	82			
No. 10	870	99			
No. 11	440	83			
No. 12	657	62		100	N/D
No. 13	960	95			
No. 14	1227	83			
No. 15	UQ (4ml)[1]	55	Lansoprazole 30	84	N/D
No. 16	200 - 600	59 - 75	Omeprazole 20	89	800 mg/kg for 14 days caused no changes in body weight and other serum biochemical parameters

Misoprostol 0.4 Misoprostol 0.4

No. 17	250 - 500	22 - 63	Ranitidine 50	51	N/D
No. 18	200- 600	9 - 36	Omeprazole 10	50	No sign of acute toxicity was observed at 2 g/kg dose.
No. 19	50 - 400	78 - 100	Omeprazole 20	80	No sign of acute toxicity was observed.
No. 20	5- 25	36-67	Cimetidine 25	39	N/D
No. 21	50 - 400	57 - 95	omeprazole 20	76	No toxicity was observed at dose of 5 g/kg for 14 days, as evaluated based on clinical and histopathological observations.
No. 22	250 - 1000	50 - 94	Ranitidine 50	97	Up to 3 g/kg body weight did not cause any toxic effect and no mortality was observed in treated rats.
No. 23	50 - 400	54 - 96	Ranitidine 50	95	Up to 3 g/kg body weight did not cause any toxic effect and no mortality was observed in treated rats.
No. 24	100 - 400	≈ 27 - 63	Cimetidine 50	≈74	N/D
No. 25	40	≈60-87	Quercetin 100	79	N/D
No. 26	100 - 400	66 - 86	Sucralfate 100	92	LD_{50} >2000 mg/kg
No. 27	125 - 500[1]	29 - 77	Ranitidine 100	81	Up to 4 g/kg caused no behavioral changes and mortality.
No. 28	8.75 – 26.25	25 - 69	N/D		N/D
No. 29	880	54	N/D		N/D
No. 30	62.5 - 500	59 - 89	Omeprazole 20	86	No sign of toxicity
No. 31	250 - 1250	38 - 73	N/D		N/D
No. 32	100	56[2], 83[3], 47[4]	Carbenoxolone 100	83	N/D
No. 33	8ml	≈ 40	N/D		N/D
No. 34	500 - 5000	72 - 100	N/D		LD50 >500 g/kg.
No. 35	0.125 – 0.5	0 - 51	N/D		N/D
No. 36	75 - 300	38 - 68	Famotidine 20	34	N/D

No. 37	125 - 500	25 - 82	Ranitidine 50	88	Up to 2 g/kg caused no mortality or behavioral changes during the period of 14-day observation.
No. 38	100 - 400	14 - 60	Omeprazole 20	55	Up to 5 g/kg caused no mortality or behavioral changes during the period of 14-day observation.
No. 39	100 - 1000	50 - 100	Omeprazole 30	67	5 g/kg caused no mortality or behavioral changes during the period of 14-day observation.
No. 40	3 – 30	≈ 17 - ≈ 50	Omeprazole 40	≈ 50	N/D
No. 41	50 - 200	15 - 82	N/D		
No. 42	500	≈60	N/D		
No. 43	50-500	41-88	Omeprazole 30	98	N/D
No. 44	25 - 500	49 - 83	Carbenoxolone 80	83	N/D
No. 45	50 - 400	60 - 94	Omeprazole 20	82	LD50 >5 g/kg; 5 g/kg body weight did not cause any toxic effect and no mortality was observed in treated rats.
No. 46	1 – 10	41 - 80	Cimetidine 100	57	N/D
No. 47	100 - 1000	32 - 72	Omeprazole 20	77	N/D
No. 48	100 - 500	90 - 97	Omeprazole 15 - 50	89 - 93	N/D
No. 49	100 - 400	≈ 5 - 22	Ranitidine 50	≈ 21	N/D
No. 50	330 - 660[5]	95 - 98	N/D		N/D
No. 51	100	25-38	lansoprazole 30	65	N/D

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No. 52	250 - 500	16 - 44	N/D		N/D
No. 53	250 - 1000[2]	0 - 89	lansoprazole 30	56	A single dose of 5 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation.
No. 54	200	48	Ranitidine 2.5	48	1g/kg once daily for 4 weeks did not produce any visible signs or symptoms of toxicity.
No. 55	30 - 300	39 - 96	Ranitidine 50	80	N/D
No. 56	250 - 1000	77 - 99	lansoprazole 30	63	N/D
No. 57	250 - 1000	46 - 88	lansoprazole 30	47	N/D
No. 58	50 - 500	75 - 87	Omeprazole 30	76	N/D
No. 59	62.5 - 500	48 - 61[1]	Carbenoxolone 100	60	N/D
No. 60	250 - 500	35 - 75	N/D		N/D
No. 61	1000 - 2000	48 - 72	N/D		LD50 = 13 g/kg
No. 62	250 - 500	20 - 40	N/D		N/D
No. 63	50 - 200	15 - 58	Ranitidine 50	≈ 75	LD_{50} > 2 g/kg; 2 g/kg caused no toxic symptoms during 14 days.
No. 64	500	39[6], 50[1], 90[7]	Omeprazole 20	80	N/D
No. 65	250 - 500	28 - 47	N/D		N/D
No. 66	300 – 1000[6]	73 - 94	Ranitidine 60	≈ 10	LD_{50} > 6 g/kg for PO and LD_{50} = 0.83 g/kg for IP
No. 67	700	40	Carbenoxolone 200	28	N/D
No. 68	200	59[1], 45[8]	Misoprostol 0.2	71	2 g/kg caused no toxic symptoms during 48 hours.
No. 69	50 - 150	69 -100	Ranitidine 50	100	5 g/kg caused no toxic symptoms during 7 days.

No.70	100	67	Sucralfate 250	72	N/D
No. 71	400	91	Omeprazole 10	93	N/D
No. 72	500	60	Carbenoxolone 200	42	N/D
No. 73	30 - 300	95 - 99	Omeprazole 40	98	N/D
No. 74	10- 50	44 - 87	Sucralfate 250	87	N/D
No. 75	25- 200	17 - 89	Sucralfate 100	74	N/D
No. 76	0.025- 0.1 ml/kg	1.15 – 2.5[9]	Ranitidine 20	1.7[9]	N/D
No. 77	10 - 100	60 - 76	Omeprazole 40	75	N/D
No. 78	700 - 2800	13 - 68	Ranitidine 27	91	N/D
No. 79	250 - 500	72 - 81	Omeprazole 20	92	2 g/kg caused no toxic symptoms during 14 days. No changes in renal and liver function in acute toxicity test.
No. 80	4 – 8	36 - 84	N/D		N/D
No. 81	10 - 100	25 - 82	Misoprostol 0.05	63	N/D
No. 82	30 - 100	49 - 63	N/D		N/D
No. 83	2.5 - 10[10]	53 - 96	N/D		N/D
No. 84	125 - 500	53 - 88	N-acetylcysteine 150	86	N/D
No. 85	5 – 20	70 - 86	Omeprazole 20	79	Single dose of extract up to 300 mg/kg caused no changes in behaviors, body weight, liver and renal function during 14-day observation.
No. 86	50 - 500	≈33 - 95	Ranitidine 50	≈10	LD_{50} > 2.5 g/kg. Up to 2.5g/kg caused no sign of toxicity during 24 hours observation.
No. 87	750[6]	100	Famotidine 20	83	N/D
No. 88	50 - 200	66 - 9	lansoprazole 30	96	N/D
No. 89	62.5 - 250	5 - 66	Carbenoxolone 100	70	Single dose of 2 g/kg caused no changes in behaviors and, body weight during 14-day observation
No. 90	100 - 400	12 - 40	N/D		N/D
No. 91	100 - 200	58 -80	Ranitidine 30	66	1 g/kg once daily for 15 days caused no sign of toxicity.
No. 92	50 - 200	NI	Ranitidine 50	NI	Single dose of extract up to 2 g/kg caused no changes in behaviors, body weight, liver and renal function during 14-day observation
No. 93	200	52	Sucralfate 500	76	N/D
No. 94	50 - 100	26 - 58	Ranitidine 50	≈70	Single dose of extract up to 2 g/kg caused no sign of toxicity during 14-day observation
No. 95	100 - 1000	63 - 95	Omeprazole 40	55	N/D
No. 96	125 - 500[1]	42 - 69	Omeprazole 10	78	N/D
No. 97	3.8 – 15.3	65 - 82	Omeprazole 3.3	68	N/D

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No. 98	62.5 - 500	0 - 76	N-acetylcysteine 750	71	Single dose of extract up to 4 g/kg p.o. did not caused any sign of toxicity during 3 days
No. 99	4.9 – 48.9	≈29 - 70	Ranitidine 50	≈70	N/D
No. 100	50 - 200	40 - 64	Misoprostol 0.05	92	N/D
No. 101	100 - 200	18 - 35	Ranitidine 50	57	N/D
No. 102	20[11]	66	Sucralfate 500	65	N/D
No. 103	100 - 400	16 - 42	N/D		N/D
No. 104	1425[1]	94	Misoprostol 0.4	100	N/D
No. 105	59.2	97	Misoprostol 0.4	100	Orally given 716 mg/kg daily for three days caused no sign of toxicity
No. 106	50 - 200	49 - 100	Omeprazole 50	92	N/D
No. 107	500	60	Sucralfate 500	65	Single dose of extract up to 2 g/kg p.o. did not caused any sign of toxicity during 14 days
No. 108	250 - 500	67 - 84	Omeprazole 40	93	Single dose of extract up to 2.5 g/kg p.o. did not caused any sign of toxicity during 14 days
No. 109		53[6]			
No. 110		86[7]			
No. 111		90[6]			
No. 112	1250[12]	90[6]	Atropine 10	86	N/D
No. 113		17[6]			
No. 114		17[7]			
No. 115		53[6]			
No. 116	100	71	lansoprazole 20	≈70	N/D
No. 117	) – 5000	25 - 88	Sucralfate 100	88	LD_{50} values of the aqueous extract = 3.04 g/kg, i.p
No. 118	125 - 500	43 - 99	Sofalcone 100	50	N/D
No. 119	430 - 1720	22 - 82	N/D		Single dose of extract up to 17.20 g/kg p.o. did not caused any sign of toxicity during 24 hours
No. 120	200 - 400	46 - 71	lansoprazole 30	71	Oral 4 g/kg daily for 14 days did not change behavior and blood cell counts.
No. 121	50 - 750	93 - 97	Omeprazole 30	96	Single dose of 5 g/kg p.o. did not caused any sign of toxicity during 14 days. LD_{50} ≥5.0g/kg, i.p
No. 122	100 - 500[13]	≈25 - 70	Omeprazole 20	≈70	N/D
No. 123	320 - 800	31 - 87	Sucralfate 100	87	N/D
No. 124	250 - 1000	84 - 81	lansoprazole 30	49	A single oral dose of 5 g/kg revealed non-toxicity in the treated animals. After 14 days of administration, no animal died and no changes in weights of body, kidney, liver, lungs and heart.
No. 125		26 - 95		23	A single oral dose of 5 g/kg revealed non-toxicity in the treated animals during 14-day observation.
No. 126	125 - 250	18 - 88	lansoprazole 30	30	
No. 127	400[1]	39	Sucralfate 500	63	N/D
No. 128	100 - 400	19 - 84	Ranitidine 50	73	A single oral dose of 4 g/kg revealed non-toxicity in the treated animals during 14-day observation.
No. 129	30 - 300	≈5 - 90	N/D		N/D
No. 130	200	24	N/D		N/D
No. 131	10	87	Omeprazole 40	92	N/D
No. 132	50 - 200	48 - 79	Carbenoxolone 100	85	500 mg/kg daily for 14-days did

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					not cause any detectable adverse effects
No. 133	100 - 200	47 - 70	Omeprazole 20	74	N/D
No. 134	20 ml	81	N/D		N/D
No. 135	100 - 400	32 - 90	Ranitidine 100	55	N/D
No. 136	100 - 800	51 - 98	Ranitidine 50	17	N/D
No. 137	30 - 300[14]	≈47 - 72	N/D		N/D
No. 138	500 (No effect at 250 mg)	97	Carbenoxolone 100	75	A single oral dose of 5 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation
No. 139	500 - 1000	43 - 75	Ranitidine 50	100	N/D
No. 140	20	81	Sucralfate 500	66	N/D
No. 141	125 - 500[2](No effect at 125 mg)	0 - 71	Carbenoxolone 100	85	5 g/kg daily for 14 days did not produce any visible signs or symptoms of toxicity including liver and renal function.
No. 142	500 - 1000	28 - 85	Ranitidine 50	81	
No. 143	200	40[15]	N/D		LD50 = 1050 mg/kg
No. 144	30 - 300	35 - 81	Omeprazole 40	72	N/D
No. 145	300	22[6], 67[2]	Omeprazole 20	61	N/D
No. 146	50 - 200	13 - 61	Ranitidine 50	57	N/D
No. 147	50 - 200	79 - 68	Carbenoxolone 100	77	A single oral dose of 5 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation
No. 148	250 - 1000	93 - 96	Carbenoxolone 250	61	4 g/kg decreased activity of mice.
No. 149	250	100	Carbenoxolone 100	86	ND
No. 150	200 - 600	94 - 100	Sucralfate 250	63	ND
No. 151	100 - 500	16 - 86	Omeprazole 30	43	A single oral dose of 2 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation
No. 152	250 - 1000	≈45 - 95	lansoprazole 30	55	5 g/kg daily for 14 days did not produce any visible signs or symptoms of toxicity including liver, kidney, heart and lungs renal function.
No. 153	500[16]	84	Pentoprazole 20	80	ND
No. 154	50 - 500	49 -78	Pentoprazole 20	80	A single oral dose of 5 g/kg did not produce any visible signs or symptoms of toxicity during 3-day observation
No. 155	5 - 15	42 - 81	Phenidone 100	91	ND
No. 156	100 - 300	68 - 72	ND		ND
No. 157	1 – 3 ml	30 - 56	ND		ND
No. 158	20	89	Sucralfate 500	63	ND
No. 159	100 - 400	82 – 42[17] 21 - 25[18]	Misoprostol 0.1	94	P.O. LD50 = 4570 2754 mg/kg for leaf extract and 2754 mg/kg root extract
No. 160	50 - 100	43 - 75	Sucralfate 200	8	ND
No. 161	2.5 - 10	34 - 100	Parthenolide 5 - 40	27 - 100	ND
No. 162	400	48	Dehydroleucodine 40	0	ND
No. 163	10 - 50	65 - 98	Sucralfate 250	82	ND
No. 164	10 - 30	66 - 74	Omeprazole 20	78	A single oral dose of up to 300 mg/kg did not produce any visible signs or symptoms of toxicity during 14-day observation
No. 165	100 - 200	66 - 71	Famotidine 20	73	A single oral dose of up to 2 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation

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No. 166	200	70	Ranitidine 50	75	ND
No. 167	50 - 200	13 - 40	Carbenoxolone 100	46	A single oral dose of up to 2 g/kg did not produce any visible signs or symptoms of toxicity during 14-day observation
No. 168	250 - 500[1]	99 - 100	Omeprazole 20	86	ND

All herbal ingredients were given orally unless otherwise indicated; NI: not indicated; ND: Non-determined; IV: intravenous injection.
[1] ethanol extract; [2]Methanolic extract; [3]Diethyl ether extract; [4]Petroleum ether extract; [5]Olive oil extract; [6]water extract; [7]Hexane extract; [8]ethy acetate extract; [9]Damage scores; [10] 3β-hydroxy-3-deoxibarbatusin fraction; [11]Cholorform extract; [12]Amount equal to raw material; [13]Astaxanthin esters;[14]Red pigment fraction; [15]In diabetic rat; [16]Acetone extract;[17] leaf' [18]Root;

Mechanisms

Although the exact mechanisms whereby herbal medicines prevent the development of gastric ulcer remain unclear, evidences suggest the antiulcerogenic benefit of herbal extracts could be via divergent mechanisms, including anti-oxidation, stimulation of PGE2 production, inhibition of acid secretion and histamine release, as well as antimicrobial properties. The potential mechanisms of some herbal ingredients are listed in Table 3.

Table 3: The Mechanisms That Herbal Extracts Prevent Gastric Ulcer

Herbal Ingredient No. (Refer to Table 1)	Anti-oxidative properties	Acid secretion	H^+/K^+ ATPase	Others
No. 1	Yes	↓	N/D	↑Mucus, ↓inflammaiton
No. 2	Yes	↓	N/D	↑Mucus, ↓Pepsin content
No. 16	Yes	N/D	N/D	↓Inflammation
No. 19	Yes	N/D	N/D	↑HSP70
No. 21	Yes	N/D	N/D	↑Glycoprotein & HSP70, ↓BAX protein
No. 22	Yes	N/D	N/D	
No. 23	Yes	↓	N/D	
No. 24	Yes	N/D	N/D	↑Non-protein sulfhydryles
No. 25	Yes	N/D	N/D	
No. 26	N/D	↓	N/D	
No. 28	Yes	↓	N/D	↑Mucus, ↑Non-protein sulfhydryles, ↓c-Jun kinase activity
No. 29	Yes	↓	N/D	↑Mucus, ↓Histamine
No. 30	Yes	N/D	N/D	↑Mucus, ↑Glycoprotein & HSP70, ↓BAX protein, ↑PGE2,
No. 31	N/D	N/D	N/D	↑ HSP70, ↓apoptosis
No. 33	Yes	N/D	N/D	↑Gastric mucosal nitrite levels
No. 35	Yes	N/D	N/D	
No. 36	Yes	N/D	N/D	↑Nitrite & nitrate
No. 37	Yes	N/D	N/D	
No. 39	N/D	↓	N/D	↑Glycoprotein, ↓inflammaiton
No. 40	(-)	↓	↓	↓Nitric oxide, Mucus(-)
No. 41	N/D	↓	N/D	↑Mucus, ↑Glycoprotein & hexasamine; ↓PGE2
No. 42	Yes	N/D	N/D	↓Mast cell and histamine content
No. 43	Yes	N/D	N/D	
No. 44	N/D	(-)	N/D	Mucus(-), ↑Hexasamine; ↓PGE2
No. 46	Yes	↓	N/D	↑Mucus, ↓Nitric oxide, ↓TNF, ↓IL-6
No. 48	Yes	↓	↓	↓Pepsin content, ↑Mucus, ↑hexasamine; ↑PGE2
No. 49	Yes	↓	↓	↑Mucus
No. 50	Yes	↓	N/D	↑Mucus, ↓Pepsin content
No. 52	N/D	↓	N/D	↑Mucus, ↑ Non-protein sulfhydryles, ↓inflammaiton
No. 55	N/D	N/D	N/D	↑Glycoprotein
No. 58	N/D	↓	N/D	

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No. 60	N/D	N/D	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 61	N/D	↓	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 62	N/D	↓	N/D	↑Glycoprotein, ↓inflammaiton, ↑Non-protein sulfhydryles
No. 63	Yes	N/D	N/D	
No. 64	Yes	N/D	N/D	↓Alkaline phosphatase
No. 69	Yes	N/D	N/D	↑Hexose, ↑Hexosamine
No. 70	Yes	↓	N/D	↑Mucus, ↓Pepsin content, ↑Hexose
No. 71	N/D	↓	N/D	↑Mucus
No. 73	N/D	N/D	N/D	Mucus(-)
No. 74	Yes	↓	N/D	↑Hexose, ↑Hexosamine
No. 75	N/D	↓	N/D	↓Pepsin content
No. 76	Yes	N/D	N/D	Antimicrobial activity, ↓inflammaiton,
No. 77	Yes	↓	↓	
No. 78	N/D	N/D	N/D	↓Inflammaiton,
No. 79	Yes	N/D	N/D	↑Mucus
No. 80	Yes	N/D	N/D	
No. 81	Yes	N/D	N/D	↑K^+ATP channel, ↑nitric oxide synthase, ↑Non-protein sulfhydryles
No. 82	Yes	N/D	N/D	↑ HSP72, ↓nitric oxide synthase, ↓inflammaiton,
No. 83	N/D	N/D	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 84	Yes	N/D	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 85	Yes	↓	N/D	↑Mucus, ↑HSP70, ↑Non-protein sulfhydryles, ↑nitric oxide, ↓BAX protein; anti-*H pylori*
No. 86	Yes	N/D	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 88	N/D	N/D	N/D	↑Glycoprotein; ↑PGE2
No. 90	Yes	↓	↓	↑Mucus
No. 91	Yes	N/D	↓	↑Mucus, anti-*H pylori*
No. 92	Yes	↓	↓	
No. 93	N/D	↓	↓	↑Mucus
No. 94	Yes	N/D	↓	↑Mucus
No. 95	N/D	↓	↓	↑Mucus
No. 96	N/D	↓	↓	↑Mucus, ↓Gastrin, ↑PGE2
No. 98	Yes	↓	N/D	↑Mucus, ↑Non-protein sulfhydryles
No. 100	Yes	N/D	N/D	↑Non-protein sulfhydryles, ↓inflammaiton
No. 101	Yes	N/D	N/D	↑Mucus, Antimicrobial
No. 102	N/D	↓	↓	↑Mucus, ↓Pepsin content, ↓Gastrin, ↑PGE2
No. 103	Yes	↓	↓	
No. 106	N/D	(-)	N/D	↑Hexosamine
No. 107	Yes	↓	↓	↑Mucus
No. 108	Yes	N/D	↓	↑Mucus
No. 118	N/D	(-)	N/D	↑Mucus
No. 120	N/D	↓	↓	↓Gastrin
No. 122	Yes	N/D	↓	↑Mucus
No. 125	N/D	N/D	N/D	↑Nitric oxide, ↓TNFα, anti-*H. pylori*
No. 127	N/D	↓	↓	↑Mucus
No. 128	Yes	↓	↓	↓Histamine content, ↑Mucus, ↓Microvascular permeability, ↑Mucosal proliferation.
No. 130	Yes	N/D	N/D	↓Inflammaiton
No. 131	Yes	N/D	N/D	↑Mucus, ↓Inflammaiton
No. 132	N/D	N/D	N/D	↑Proliferation, ↓Nitric oxide, antimicrobials
No. 135	N/D	↓	N/D	Mucus(-)
No. 138	Yes	N/D	N/D	Anti-hemorrhagic effect, antimicrobials, ↑PGE2
No. 139	N/D	↓	↓	
No. 140	Yes	↓	↓	↑Mucus, ↑PGE2
No. 141	N/D	N/D	N/D	↑Nitric oxide, ↑Proliferation, ↑PGE2, ↑COX-2 expression
No. 144	Yes	N/D	N/D	↑Proliferation,
No. 146	Yes	N/D	N/D	↑Mucus
No. 147	Yes	(-)	N/D	Mucus(-)
No. 149	（-）	N/D	N/D	↑Mucus, ↑HSP70，↑PGE2, anti-*Helicobacter pylori*

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No. 150	N/D	(-)	N/D	↑Hexosamine
No. 156	N/D	↓	N/D	↑Mucus, ↓Histamine,↓inflammaiton
No. 158	Yes	↓	↓	↑PGE2
No. 163	Yes	↓	N/D	↓Pepsin content, ↑Proliferation, ↑Hexosamine
No. 164	Yes	↓	N/D	↑Mucus, ↑HSP70, ↑ Non-protein sulfhydryles, ↑Nitric oxide, ↓COX-2, anti-*Helicobacter pylori*
No. 166	Yes	↓	N/D	↓Pepsin content,
No. 168	Yes	↓	N/D	↑Mucus

PGE2: prostaglandin E2; HSP70: 70 kilodalton heat shock protein; COX-2: cyclooxygenase-2. (-): No effect.

a. Antioxidant

The development of gastric ulcer is associated with oxidative stress. An increase in lipid peroxidation and reduction of catalase were observed in mucosal tissue of gastric ulcer (Tandon et al., 2004). Consistently, the glutathione levels were lower while malondialdehyde (MDA), an oxidative product, levels were higher in mucosal tissue of gastric ulcer (Demir et al., 2003). Certain antiulcerogenic herbal ingredients exhibit antioxidant benefits. For example, *Morus alba* extract significantly increased the enzyme levels of SOD, GR and GRX in ethanol-induced gastric ulcer (Ahmad et al., 2013). *Jasminum sambac* extracts prevented the decrease in SOD activity and reduction in MDA levels in the stomach of ethanol-induced gastric ulcer (Alrashdi et al., 2012). The SOD activity and MDA levels in rats pre-fed with *Jasminum sambac* extracts were comparable to those pre-fed with omeprazole (Alrashdi et al., 2012). In an ethanol-induced gastric ulcer model, *Corchorus olitorius* leaf extract at a dose of 400mg/kg body weight was more effective on SOD activity and MDA levels compared to omeprazole (Al Batran et al., 2013). Thus, antioxidation could be one mechanism by which herbal ingredients prevent the development of gastric ulcer.

b. Inhibition of Inflammation

Gastric ulcer is accompanied by mucosal inflammation, which is particularly important for recurrent gastric ulcer (Watanabe et al., 2002). Certain herbal ingredients inhibit mucosal inflammation. It has been reported that methanolic extract of *Boesenbergia rotunda* inhibited leucocyte infiltration into gastric wall in ethanol-induced gastric ulcer (Abdelwahab et al., 2011). Prior to induction of gastric ulcer with ethanol, oral administrations of American ginseng extract at daily doses of 250, 500 and 1250 mg/kg for 28 days, IL-1β protein levels were significantly decreased by 29.3%, 27.5% and 54.4%, respectively, compared with vehicle treatment (Huang et al., 2013). Orally given chelerythrine, an active constituent of antiulcerogenic agent (Papaveraceae), at a dose of 5 mg/kg once daily for 4 days also significantly reduced pro-inflammatory interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) level in both gastric mucosa and serum, and inhibited the infiltration of inflammatory cells (Li et al., 2014). Even the short term administration of herbal ingredient inhibits mucosal inflammation, too. For example, orally given ethanol extracts of *Artemisia asiatica* one hour prior induction of gastric ulcer with ethanol significantly reduced the levels of mucosal IL-1β and INFγ while the anti-inflammatory cytokine, IL-10, was significantly increased (Park et al., 2008). Additionally, oral extracts of himalayan cinquefoil or Sukari date markedly reduced the levels of mucosal histamine (Al-Qarawi et al., 2005; Laloo et al., 2013) and microvascular permeability (Laloo et al., 2013). Hence, anti-inflammation could be another mechanism by which herbal ingredient's ingredients prevent the development of gastric ulcer.

c. Antimicrobials

H. pylori infection is one of the causes for gastric ulcer (Arroyo et al., 2004; Chen et al., 2010). Antibiotics are effective in the management of gastric ulcer (Sereni et al., 2012). Certain antiulcerogenic herbal ingredients exhibit antimicrobial properties. Sidahmed et al. (2013) reported that the antiulcerogenic agent, an extract of mitrella kentii bark, inhibited *H. pylori* J99 with a minimum inhibitory concentration (MIC) of 125µg/ml. Similarly, the extract of swallow root, another antiulcerogenic ingredient, displays a MIC of 150 µg /mL against *H. pylori* isolated from patients with gastric ulcer (Srikanta et al., 2007). A similar anti-*H pylori* activity was also observed by *Davilla nitida* extract with a MIC of 125 µg /mL (Kushima et al., 2009). A more potent antibacterial efficacy was shown by the methanolic extract of *Mouriri elliptica Martius* with a MIC of 0.025µg/mL (against *H. pylori* isolated from patients with gastric ulcer) (Moleiro et al., 2009). Interestingly, acetate fraction from *Byrsonima fagifolia* did not only inhibit *H. pylori*, but also inhibited *Escherichia coli* and *Staphylococcus aureus* with a MIC of 250 µg /mL (Lima et al., 2008). Thus, the antibacterial properties of certain herbal ingredients could represent additional mechanism by which herbal ingredient's ingredients prevent the development of gastric ulcer.

d. PGE2

The levels of mucosal prostaglandin E2 (PGE2) are lower in gastric ulcer (Okazaki et al., 2007) and administration of PGE2 accelerates the healing of gastric ulcer (Kobayashi et al., 1982). Pre-fed rats with *Pithecellobium dulce* extract at a dose of 200 mg/kg daily for 30 days prevented the reduction of mucosal PGE2 with an efficacy comparable to 30 mg/kg of omeprazole (Megala and Geetha, 2012). One hour prior to induction of ulcer, orally giving the extract of *Anacardium humile St. Hil* induced an over 3-fold increase in mucosal PGE2 levels (Luiz-Ferreira et al., 2010). Moreover, oral *Tectona grandis* extract induced an over 50% elevation in mucosal PGE2 levels in an ethanol-induced gastric ulcer model (Singh et al., 2010). In contrast, some antiulcerogenic herbal ingredients decrease mucosal PGE2 levels (Motilva et al., 1994; Pérez Guerrero et al., 1994), suggesting that long term administration of certain herbal ingredients may not benefit gastric ulcer.

e. Others

Bcl-2 and Bcl-xL belong to the bcl-2-related gene family and act as broad anti-apoptotic factors extending both normal and tumor cell survival (Lei et al., 2003). Bcl-2 and Bcl-xL can inhibit apoptotic death primarily by controlling the activation of caspase proteases (Newmeyer et al., 2000). Study showed that one hour prior to induction of gastric ulcer with ethanol, orally given 500 and 1250 mg/kg of American ginseng extract increased Bcl-xL protein levels by 1.97- and 2.69-fold , respectively, compared with vehicle treatment. In addition, the expression of p-Bad was significantly increased in a dose dependent manner following treatment with ginseng extract (Huang et al., 2013). Consistently, oral ginseng extract inhibits apoptosis in an ethanol-induced gastric ulcer model (Yeo et al., 2008). In contrast, oral antiulcerogenic herbal ingredients stimulate mucosal proliferation (Laloo et al., 2007; Potrich et al., 2010).

Acid secretion is involved in the pathogenesis of gastric ulcer. Inhibition of proton pump is effective to treat gastric ulcer via reducing acid secretion. Studies showed that numerous antiulcerogenic herbal ingredients inhibit H^+/K^+ ATPase and reduce acid secretion. For example, oral *Pithecellobium dulce* extract for 30 days raised the pH levels in gastric juice and lowered H^+/K^+ ATPase activity comparable to normal levels (Megala and Geetha, 2012). Oral *cinnamomum tamala* leaf extract twice daily for 5 days caused a 50% reduction in H^+/K^+ ATPase activity (Eswaran et al., 2010). Moreover, mucus protects gastric wall from damage while pepsin damages gastric wall (Venables, 1986). Certain antiulcerogenic herbal ingredients either increase gastric mucus content (Chen et al., 2005; El-Dakhakhny et al., 2000; Golbabapour et al., 2013; Motilva et al., 1994) or lower pepsin content (Megala and Geetha, 2012; Sun et al., 1991), or both (Ahmad et al., 2013; Alam et al., 2009; Goel et al., 2005). And some antiulcerogenic herbal ingredients increase hexasamine (Devi et al., 2007; Megala and Geetha, 2012; Pérez Guerrero et al., 1994) or non-protein sulfhydryles content (Al-Howiriny et al., 2003 and 2005; Al-Rehaily et al., 2002). Collectively, herbal ingredients prevent the development of gastric ulcer via divergent mechanisms.

Conclusions

Herbal ingredients can effectively prevent the development of gastric ulcer via multiple mechanisms. Antiulcerogenic herbal ingredients are safe and some antiulcerogenic herbal ingredients, such as date, pomegranate, and bitter melon are edible. Use of these ingredients could be an alternative approach to reduce the risk of gastric ulcer, in particular, for those people who frequently drink alcohol. For subjects with *H pylori* positive, administration of herbal ingredients with anti-*H pylori* properties, such as *Mitrella kentia*, citrus lemon, and *Cratoxylum arborescens (Vahl) Blume* along or in combination with other herbal ingredients could be an optional regimen to prevent the development of ethanol-induced gastric ulcer. Of course, randomized double blinded clinical trial is required before the herbal ingredients can be widely deployed in clinical settings.

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