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# A Comprehensive Review of the Marketed Antiulcer Polyherbal Formulations

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**Abstract:** An imbalance in the aggressive factors and protective factors in the gastrointestinal tract leads to peptic ulcers. Modern medicinal prescriptions for ulcers involve the use of allopathic drugs. However, several disadvantages, such as side effects, discordancy, and altered physiological aspects, have led to the quest for alternative safer medications. The use of herbs to treat ulcers has been practiced for decades in Ayurveda. A combination of such herbs, known as polyherbal formulation, shows several advantages like synergistically augmented beneficial effects, better patient compliance, and reduction in dose of individual drugs without compromising the therapeutic effects. In recent years, this valuable traditional knowledge of the medicinal values of herbs, along with current value-added developments, has ensured the usage of improved Ayurvedic medicine in a milieu of treatments. In the last two decades, many polyherbal formulations have been developed and evaluated for their antiulcer potential. The advancements in analytical methods have even led to the isolation of the phytoconstituents from crude herbal drugs, and their benefits in therapeutics have been studied. The core aim of the current review is to enlighten the comprehensive overview of the composition of some marketed antiulcer polyherbal formulations and the preclinical models to prove their gastroprotective potentials based on scientific findings.

**Keywords:** *Antiulcer, Ulcer, Phytoconstituents, and Polyherbal formulations*

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## 1. INTRODUCTION

Peptic ulcer is the foremost common ailment of the gastrointestinal tract affecting an expansive populace throughout the world. The treatment of ulcers, along with their associated complications has added to the socioeconomic burden.[1] Ulcer is displayed in terms of injuries of the parts of the gastrointestinal tract uncovered to acid and pepsin.[2] The pathology of ulcers is understood to be a consequence of inequity amid the shielding and hostile factors of the gastrointestinal tract.[1] The defensive factors are gastroprotective prostaglandin, bicarbonate, endogenous nitric oxide, mucus secretion, and normal tissue blood supply. The aggressive factors include acid, free radicals, pepsin, abnormal motility, bile salts, NSAIDs, alcohol, and *H. pylori*.[2] The prolonged lesions may lead to further problems such as gastric bleeding, impediment, and damage.[3] Currently, the widespread use of drugs belonging to the class anticholinergics, proton pump inhibitors, histamine receptor antagonists, antacids, ulcer protectives, and antibiotics are being further encouraged in for the treatment of peptic ulcers.[2,4] Serious side effects such as hepatotoxicity, thrombocytopenia, nephrotoxicity, and impotence have been recorded after prolong use of these drugs. These undesirable effects have given rise to a need for more viable and secure choices for the treatment of ulcers.[4] A recent trend has been observed in the use of phytopharmaceuticals as an alternate medicine. *Aegle marmelos, Azadirachta indica, Carica papaya, Allium sativum, Acacia arabica,* and *Balsamodendron Mukul* are a few traditional herbs being proven scientifically to contain such phytoconstituents and possess antiulcer activities.[5] Traditionally, the Ayurvedic literature Sharangdhar Samhita acknowledges herb-herb combinations for therapeutics. For a long time, numerous such polyherbal formulations (PHFs) have been developed, and their use against pathologies of different origins was endorsed.[6] Further, the advances in analytical techniques have led to the isolation of several phytoconstituents such as 7,8-dihydro-8-hydroxypalmatine, Atropine, Cocaine, Matrine,[7] Thymoquinone,[8] Costunolide[9] to evaluate their therapeutic potential in peptic lesions. Two main principles that form the basis for Ayurvedic formulations are the use of a single herb or a combination of more than one herb.[9] Such use of combined plant extracts are preferred over single ones and nowadays, most Ayurvedic preparations are polyherbal. The foremost benefit of merging multiple herbs is the positive interaction leading to synergism. While the individual herbs contain various constituents in minute quantities, the combination may sum up their activities to yield a greater potency. Furthermore, certain activities of phytoconstituents are noteworthy as they were effective when potentiated by another herb but truant when utilized alone. Bringing down the dosage of an individual component of the PHF due to synergism moreover leads to a diminishment of the harmful side effects. The comfort of the patient is additionally improved by disposing of them ought to take more than one medication concurrently which by implication results in superior compliance and restorative effects. Such advantages have driven to extend the ubiquity of the PHFs over single herb formulation. However, polyherbal preparations also possess certain limitations. The major drawback is incompatibility among the components, which may be quantitative, energetic, or functional in nature. Allopathic drugs utilized concomitantly might result in drug-herb interactions. The reproducibility in clinical responses might be troublesome to attain with herbal preparations.[9] Ayurvedic medicines were traditionally manufactured by the physicians themselves, or the nearby villagers were directed to collect the remedial plants for curative, preventive, and corrective drives. In the olden days, the dosage forms of Ayurvedic medications such as bhasma, churna, asava-arista, sindoor extract, Vati, decoction, gutika, and medicated oil were used. However, in modern times the advancement in the industrial infrastructure has played a revolutionary role in developing the Ayurvedic formulations into capsules, syrups, tablets, and salves.[10]

## 2. HERB-HERB COMBINATION

Plant materials of ethnomedicinal significance in both crude and prepared forms have been utilized in therapeutics for decades. Use of herbal combinations is favored over using a single herb in therapy owing to the inadequate therapeutic effects of individual herbs. The organization of the ethnobiological components into a certain formula has appeared to possess likely interactions. These interactions would be consequent of mutual assistance, mutual antagonism, mutual enhancement, and mutual restraint.[12] These interactions have either favorable or undesirable consequences, which include potentiation, reinforcement, restraint, counteraction, detoxification, and incompatibility.[13]

### *2.1 Benefits of Herb-Herb Combination*

Polyherbal formulations designed by the combination of multiple herbs exhibit ample advantages over a single herb and allopathic medicine. This resulted in the emerging trend in herbal drug therapy worldwide.

- High therapeutic effectiveness against a vast number of afflictions is exerted owing to the presence of numerous phytoconstituents. Factual assessments show an inclination for herbal preparations due to their adequacy and promising outcomes of the treatment.[9]
- The existence of multi-components in the combination serves to potentiate the action of one drug by another. This enhancement in activity may not be attainable by individual components when utilized alone.[10]
- Polyherbal formulations have a widespread therapeutic window. Being viable indeed at a lower dose and harmless at a higher dose, most of them have a predominant risk-to-benefit ratio.[9]
- Due to synergism, polyherbal preparations are desirable. They can be prescribed at a lower dose to accomplish the required pharmacological action. This results in decreasing the possibility of harmful side effects as compared to allopathic medication.[9,10]
- By abolishing the need to administer more than one single herbal formulation at a time, polyherbal preparations bring enhanced convenience for patients. As the administration of multiple herbs as one formulation shows better convenience, it indirectly marks improved patient compliance.[10]
- Herbal combinations with a number of constituents simultaneously act on diverse targets to elicit intensive alleviation. The presence of distinctive types of constituents remedies the affliction by distinctive mechanisms to provide a complete treatment against an illness.[10]
- Having a natural source, developing a polyherbal formulation is economical and it is easily available. Global demand for PHF has increased due to

accessibility and affordability, especially in developing countries.[9]

- Synergism could be attained at the pharmacokinetic or pharmacodynamic level. Pharmacokinetic synergism is seen when the absorption, distribution, metabolism, and elimination of one herb are facilitated by another in the combination. Pharmacodynamic synergism is achievable by targeting active principles from multiple components toward common physiological systems.[9,10]

### *2.2 Limitations of Herb-Herb Combination*

A combination of herbs may not always be superior to a single herb in that certain situations may exert antagonistic effects.

- Possible chemical incompatibility might be exhibited by the combination of herbs which may lead to instability and consequently loss of therapeutic benefits.[10]
- Inappropriate use or preparation of Ayurvedic formulation may lead to adverse effects, as reported in Charaka Samhita. Concomitant use of the allopathic drug along with the Ayurvedic preparation has been increasing, which is unknown to the medical practitioner. Such use of medication of diverse origins might result in possible drug- herb interactions to accelerate harmful impacts on the patient's well-being.[9]
- It is difficult to achieve clinical reproducibility with Ayurvedic PHFs. Despite the standards available, several factors such as habitat, harvesting conditions, the season in which the herbs grow, storage conditions, and diverse manufacturing processes can affect the lack of reproducibility in the quality of the finished product. Therefore, batch-to-batch variation is a common occurrence, and it affects the safety and efficacy of the preparation.[9]
- Toxicity is another concern with respect to the presence of heavy metals like mercury, even in trace amounts. Hepatotoxic, nephrotoxic, hematotoxic and neurotoxic consequences have been reported due to these elements.[9]

The present review is a compilation of some marketed polyherbal formulations. The components and their antiulcer models, along with the parameters considered, are talked about in brief (Table 1).

## 3. PHFS WITH ANTIULCER POTENTIAL

### *3.1 Yelathy Chooranam*

Yelathy Chooranam is a Polyherbal antiulcer Siddha formulation that contains seven drugs *viz*, *Taxus buccata, Piper nigrum, Eletaria cardamomum, Syzygium aromaticum, Cinnamomum zeylanicum, Zingiber officinale,* and *Curcuma angustifolia* (Arrowroot). Several therapeutic roles of the ingredients have been detailed within the Siddha framework of medicine. The components of the polyherbal formulation are proven to possess the antiulcer potential against the various models. Petroleum ether fractions and methanolic extracts of *Eletaria cardamomum* significantly inhibited ulcers in Aspirin-induced and ethanol-induced acute ulcer models. Ethanol-induced lesions were reduced by *Syzygium aromaticum*. Orally administered *Ferula foetida* along with *Piper nigrum* dose-dependently attenuated cysteamine-induced duodenal lesions in rat models. *Cinnamomum zeylanicum* suspension reduced the ulceration intensity in the indomethacin-induced ulcer rat models. Anti-inflammatory and antinociceptive activities of lignan components of *Taxus buccata* were demonstrated by lessening the generation of TNF and cytokines. Reduction in the gastric damage induced by indomethacin evidenced the gastroprotective effect of *Zingiber officinale.* The authors reclaimed the demonstrated antiulcer effects of Yelathy Chooranam.[14]

### *3.2 NR-ANX-C*

NR-ANX-C is a PHF marketed by Natural Remedies Pvt. Ltd., Bangalore, India, constituting *Camellia sinensis, Withania somnifera, Ocimum sanctum,* shilajit, and Triphala. Significant antioxidant properties have been demonstrated by these components. *Ocimum sanctum*, and *Withania somnifera,* hold anti-ulcerative potential for which they have been used in Ayurvedic Rasayana. Triphala has been a major contributor toward exhibiting gastric care. Further, on the basis of implications of free radicals, acidity, and loss of mucosal defense as the contributing factors to ulcerations, the polyherbal formulation was assessed for antiulcer activity. The experimental protocol included Aspirin and Pyloric ligation-induced gastric lesions with the determination of ulcer index, malondialdehyde (MDA), gastric pH, gastric volume, total acidity, and adherent gastric mucus using Ranitidine (27 mg/kg *p.o.*) and Omeprazole (1.8 mg/kg *p.o.*) as standards. The results indicated that the higher doses (25 and 50 mg/kg *p.o.*) of the PHF produced a substantial reduction in MDA levels, the volume of gastric juice, and the total acidity of gastric juice in a dose-dependent manner. There was a noteworthy rise in gastric pH and adherent gastric mucus by the formulation. Additionally, higher adequacy was shown by the PHF than the standard in the decrease of gastric ulcers. The results of the study concluded that the antisecretory, cytoprotective and antioxidant actions of NR-ANX-C were accountable for the antiulcer activity.[15]

### *3.3 Livina*

Livina polyherbal capsule manufactured by Dey's Medical Stores (Mfg.) Ltd. contains *Solanum nigrum, Holarrhena antidysenterica, Tephrosia purpurea, Andrographis paniculata, Phyllanthus niruri, Tinospora cordifolia, Terminalia chebula, Asteracantha longifolia, Alstonia scholaris, Berberis aristata, Cichorium intybus,* and *Picrorhiza kurroa.* The polyherbal formulation was evaluated for its antiulcer potential against ethanol-induced ulcers. Although the pathogenic mechanisms are not well understood, ethanol is a recognized contributor to gastric mucosal injury. Lipid peroxidation due to ethanol-generated free radicals induces oxidative damage. The experimental design tested the methanol extract of Livina powder at the dosage levels of 50, 100, and 200 mg/kg *p.o.* for the determination of ulcer index, total acid, free acid, gastric volume, and gastric juice pH. Morphological examination disclosed the presence of an obvious gross mucosal lesion, including petechial lesion and long hemorrhage bands. Pre-treatment with Livina displayed extremely mild lesions with interstitial hemorrhage or an altogether absence of lesions. Significant microscopic changes were also observed in the ethanol-treated and Livina pre-treated rats. Segmental mucosal necrosis of gastric epithelium, edema, mucosal hemorrhage, and ample infiltration of leukocytes was detected in the submucosa. While the pre-treated rats exhibited only patchy mucosal epithelial loss. Livina (200 mg/kg *p.o.*) significantly reduced the ulcer index, total acid, free acid, and gastric volume in the ethanol-induced ulcer model when

compared with Ranitidine (50 mg/Kg *p.o.*) as standard. There was also a significant surge in pH when related to the ethanol-treated group.[16]

### *3.4 RO12*

RO12 is a PHF marketed by Rumi Herbal Research Institute Private Limited, Chennai. It contains the aqueous extracts of *Rosa damascena, Glycyrrhiza glabra, Aegles marmelos, Eletteria cardomum, Citrus aurantifolia, and Saccharum officinarium*. Antiulcer properties of *Aegles marmelos, Citrus aurantifolia,* and *Glycyrrhiza glabra* have been previously reported. Whereas *Eletteria cardomum* and *Glycyrrhiza glabra,* have been investigated and reported to possess antioxidant activity. Aqueous extract of the PHF was subjected to preliminary phytochemical evaluation. Following OECD guideline 423, acute toxicity testing was carried out and observed to be safe up to 2000 mg/kg. The high and low (400 mg/kg and 200 mg/kg *p.o.*) doses of PHF were subjected to antiulcer activity by Pyloric ligation- and Ethanol-induced ulcers. Ulcer induction in pylorus ligation is implicated by autodigestion of mucosa by gastric juices, reduction in the blood flow to the mucosa, and mucosal barrier breakdown. The statistical analysis of the results obtained represented a significant decrease in ulcer score and index in comparison with the standard group receiving Ranitidine (50 mg/kg *p.o.*). The 200 m/kg dose of aqueous extract of RO12 showed a substantial decline in total acidity, free acidity, total protein, and pepsin content. In comparison, the high dose reduced the total acidity, free acidity, and pepsin content while increasing the total protein content. Histopathological examination of sections from stomachs was fixed and stained with haematoxylin and eosin for microscopic observations. The study established the gastroprotective action of the PHF as a consequence of antisecretory, antioxidant, cytoprotective, increase in the bicarbonate, and blood circulation.[17]

### *3.5 Avipattikar Churna*

Avipattikar churna is a PHF marketed in Nepal constituting *Terminalia bellerica, Zingiber officinale, Vida Lavana, Piper nigrum, Emblica officinalis, Amomum subulatum, Piper longum, Terminalia chebula, Operculina terpethum*, *Cyperus rotundus, Embelia ribes, Syzgium aromaticum, Cinnamomum tamala,* and Sharkara. All the components have been established for antiulcer activity. *Piper nigrum, Terminalia chebula,* and *Piper longum* exhibit cytoprotective action on the gastric mucosa. *Zingiber officinale* is found to diminish gastric secretion, intensify the mucosal resistance and potentiate the protective aspects of the gastric mucosa. *Syzgium aromaticum* aids in the maintenance of the gastric mucosal blood supply and increases gastric mucus secretion. In the present study, the gastric ulcer was induced using Shay's pyloric technique. The gastroprotective property of Avipattikar churna was evaluated by administering the drug in two doses (500 mg/Kg and 750 mg/kg *p.o.*) against Ranitidine (25 mg/kg *p.o.)* as standard. Parameters studied include the volume of gastric content, acidity, pH, ulcer score, length of ulcer, number of ulcers, curative ratio, gastric irritancy size, and gastric irritancy index. The sum of lengths of all the ulcers in an individual stomach was designated as gastric irritancy size. The product of gastric irritancy size and ulcer number denoted gastric irritancy index. Histological examination of the gastric tissue revealed pus formation, dead neutrophils, and fibrinopurlent exudates in the control group. Avipattikar churna treated groups displayed ulcer healing with only a few inflammatory cells. Less distortion in the architecture of gastric mucosa was seen in the Ranitidine-treated group. The findings of the study revealed that the lower dose of churna holds significant antisecretory and gastroprotective effects when compared with the control. However, the results of groups treated with churna in comparison to groups treated with Ranitidine were not statistically significant.[18]

### *3.6 VRC/AS/014 Syrup*

VRC/AS/014 syrup is a polyherbal formulation marketed by Vasu Research Centre, Vadodara, consisting of *Emblica officinalis, Asparagus racemosus, Glycyrrhiza glabra, Hemidesmus indicus, Centella asiatica, Terminalia chebula, Terminalia belerica, Ipomoea turpethum, Sodii carbonas,* and Black salt. Most of these components are reported to possess antiulcer action but the preclinical assessment of the formulation is missing. The acute toxicity testing of the formulation was performed by step-up, step-down procedure following OECD guideline 423. Several *in-vitro* and *in-vivo* investigational models were utilized to evaluate the acid-neutralizing and antiulcer potential. *In vitro* acid neutralizing capacity, prokinetic activity, and astringent properties were assessed. Aspirin plus pylorus ligation induced ulcer model was utilized to evaluate the antiulcer potential of the PHF (2 and 4 mL/kg *p.o.*), having evaluated the parameters, for instance, ulcer index, total acidity, the volume of gastric secretion, and gastric wall mucus content. A decrease in ulcer index, whereas rising pH and mucus content displayed gastroprotective effects. The higher dose (4 mL/kg) showed significant antiulcer and antisecretory properties equivalent to the standard Sucralfate (300 mg/kg *p.o.*). The findings of the present work provided the preclinical scientific data to support the basis for the clinical use of VRC/AS/014 syrup. Moreover, the formulation is void of aluminium or magnesium usually present in the antacids, thus representative of the slightest impacts on the absorption and digestion.[19]

### *3.7 Digitrall*

Digitrall is a PHF marketed by M/s. S. C. Pharmaceuticals Ltd., Kolkata. The composition of the same includes aqueous extracts of *Amomum sabulatum, Foenieulum vulgar, Zingiber officinale, Piper nigram, Berberis aristata, Ptychotis ajowan,* and *Carica papaya.* The present study was performed to assess the outcome of Digitrall on the inhibition of gastric ulcers. Compared with Ranitidine (50 mg/kg) as standard, Digitrall in the doses of 1, 2, and 4 mL/kg *p.o.* showed a critical decrease in the indomethacin-induced gastric mucosal damage. Indomethacin raises the leukotrienes and 5-lipoxygenase production due to inhibition of enzyme cycloxygenase. These act as mediators for the pathogenesis of ulcers. Further complications are accentuated due to reactive oxygen species such as hydroxyl radical, hydrogen peroxide, and superoxide anion which damage the gastric lining. The referred study revealed a dose-dependent decrease in MDA, an increase in the levels of SOD, and reduced glutathione in the gastric mucosal tissue. The authors concluded that the antioxidant activity of Digitrall might be accountable for the component of antiulcer action.[20]

### *3.8 Pepgard Syrup*

Pepgard syrup is a proprietary Ayurvedic PHF of Vital Care Pvt. Ltd., Vadodara. *Glycyrrhiza Glabra, Asparagus racemosus, Astoneman indicum, Emblica officinale, Centella asiatica, Ipomoea turpethum, Syzygium aromaticum, Fumaria officinalis,* and *Coriandrum sativum* are the components of the syrup. It is

widely prescribed as an antacid for drug-induced gastritis, heartburn, gastroesophageal reflux disease (GERD), and non-ulcer dyspepsia. The test dose was computed by extrapolation of human dose with regard to body surface area based on the standard table of Paget and Barnes. The fundamental pathology of ulcerogenic injuries caused by Aspirin was attributed to coordinate impacts or discharge of reactive species. Impedances with defensive capacities such as mucus production, bicarbonate generation, and blood circulation was found to modify the gastric mucosa. The antioxidant activity of the alcoholic extract of the formulation was carried out by DPPH and hydrogen peroxide ($H_2O_2$) scavenging methods. The antiulcer potential of the alcoholic extract of the formulation (1, 2, and 4 mL *p.o.*) was evaluated using the Aspirin-induced ulcers model. Results revealed a significant reduction in the concentration of DPPH and $H_2O_2$ radicals by increasing the dose of alcohol extract of Pepgard syrup and Ascorbic acid, as a reference standard. In comparison with Ranitidine (100 mg/kg *p.o.*) used as standard, a dose-dependent rise in the antiulcer potential was also seen. The authors concluded that the existence of phytobiological constituents such as terpenoids, alkaloids, tannins, saponins, flavonoids, and glycosides could be partially responsible for the cytoprotective effects of Pepgard syrup. The possibility that the gastroprotective impact might be intervened by antioxidant action was raised.[21]

### *3.9 Amlapitta Mishran Suspension*

Amlapitta Mishran is a herbo-mineral suspension, manufactured by Shree Dhootapapeshwar Limited, Mumbai containing *Adhatoda vasica, Tinospora cordifolia, Azadirachta indica, Swertia chirata, Eclipta alba, Trichosanthes dioica, Glycyrrhiza glabra, Phyllanthus emblica, Terminalia chebula, Terminalia belerica, Shouktik bhasma,* and *Fumaria indica* as active ingredients. Antiulcer activity in various models had been established for all the ingredients. Antioxidant activity had been exhibited by *Fumaria indica,* which would aid in scavenging ulcer-induced reactive species. Indomethacin-induced ulcer model was utilized to test the antiulcer potential of polyherbal suspension at 1.35 and 2.7 mL/kg *p.o.* doses with Ranitidine (100 mg/kg *p.o.*) as standard. The reduction in ulcer index and percent inhibition findings lead to the conclusion that the Amlapitta Mishran suspension possesses significant gastroprotective potential. Enhancement in the production of prostaglandins might be capable of the avoidance of ulcers by Amlapitta Mishran.[22]

### *3.10 Hingwashtak Churna*

Hingwashtak churna is a PHF consisting of *Piper nigrum, Nigella sativa, Ferula foetida, Zingiber officinale, Cuminum cyminum, Piper longum, Trachyspermum ammi,* and Saindhava lavana. It is used as an antacid, carminative, digestive, and astringent. *Piper nigrum, Nigella sativa, Ferula foetida,* and *Zingiber officinale were* reported potent antioxidants. While *Piper longum, Ferula foetida,* and *Zingiber officinale* had been reported to enhance mucin secretion and reduce stomach cell shedding. The chloroform water extract (750 mg/kg p.o.) of the formulation was subjected to antioxidant activity by DPPH, nitric oxide, lipid peroxidation assay, and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) assay. Acute toxicity studies were performed at various dose levels. The mice were persistently watched for neurological, autonomic, and behavioral changes amid 2 hours. Any lethality was noted within 72 hours. Ibuprofen- and ethanol-induced ulcer models were utilized for the assessment of the gastroprotective study of the extract with Ranitidine (2.5 mg/kg *p.o.*) as standard. From the results, the authors concluded that the antioxidant property was shown by the PHF in a dose-dependent manner. The harmless dose of the formulation was recorded to be 10000 mg/kg. Evaluation of the parameters such as ulcer number, ulcer size, and ulcer index revealed the significant antiulcer property of Hingwashtak churna. The antioxidant ingredients and increased prostaglandin level may well be attributive to the assurance from damage.[23]

### *3.11 Qarahine*

The constituents of Qarahine, a polyherbal formulation of Hamdard laboratories, Pakistan, include *Glycyrrhiza glabra* Linn., *Cochlospermum gossypium* DC., *Lapis lazuli, Koalinum ponderosum*, *Pistacia terebinthus* Linn., silicate of magnesia, magnesium silicate, and ferrum. The PHF is prescribed for the management of amoebic and bacillary dysentery, acute and chronic gastritis, and diarrhea. One of the ingredients, *Glycyrrhiza glabra,* had been proved to possess antiulcerogenic potential. The antiulcer potential was evaluated using Aspirin and ethanol-induced ulcer models. The pH and ulcer index of standard Omeprazole (20 mg/kg *p.o.*) and Qarahine (250, 500 and1000 mg/kg *p.o.*) were compared and analyzed by One-way ANOVA. The study concluded the significant diminution in ulcer index and increase in pH of gastric content with maximum protection at 500 mg/kg dose. The protection against ulceration was seen parallelly in both models. Diminution of the number of lesions, the severity of the injury, and ulcer index was found to be substantial as compared to control.[24]

### *3.12 Phy-Blica-D*

A traditional Thai polyherbal infusion, Phy-Blica-D, consisting of *Glycyrrhiza glabra, Aegle marmelos, Phyllanthus emblica, Terminalia arjuna, Terminalia bellirica, Cyperus rotundus, Maerua siamensis, Terminalia citrina, Piper retrofractum, Zingiber officinale, Alpinia galanga, Solanum torvum, Allium sativum,* and *Tinospora crispa* as constituents. Phy-Blica-D is a rejuvenating formula of THP-R016 or Phy-Blica-O with high content of flavonoids and phenols, thereby exhibiting strong antioxidant activity. However, obnoxious odor and strong bitter taste were the impediments to the potent original formula. Slight adjustments of the formula yielded superior sensory acceptability without any compromise in the antioxidant action. Oxygen radical antioxidant capacity (ORAC) assay was the *in vitro* antioxidant activity method used to establish the antioxidant potential of Phy-Blica-D aqueous extract. Omeprazole (20 mg/kg *p.o.*) was used as a standard to compare the antiulcer activity of Phy-Blica-D aqueous extract (500 and 1000 mg/kg *p.o.*) by Ethanol-induced acute gastric lesions. The study findings revealed that both doses of the PHF significantly decreased the gastric ulcer index (UI). There is no change in the pH of gastric juice however, there is a significant rise in the levels of GSH, SOD, and CAT. The pre-treatment with extract also showed noticeable reductions in MDA activity and inducible nitric oxide synthase (iNOS) levels as compared to vehicle control. Thus the authors concluded that the concealment of oxidative stress and a rise in antioxidant activity could be responsible for the mechanism of the gastroprotective effect of Phy-Blica-D. As reported in the earlier findings, the phytoconstituents possessed free radical scavenging and gastroprotective effects, which could be responsible for the therapeutic benefit of the formulation.[25]

### *3.13 Normacid Syrup*

Normacid syrup (marketed by Ayurlab herbals Pvt. Ltd., Vadodara) is composed of *Ficus glomerata* Roxb., *Fagonia Arabica* L., *Vetiveria zizanioides* Stapf., *Santalum album* L., *Andrographis paniculata* Nees., *Melia azadirachta* L., *Terminalia bellerica* Roxb., *Emblica officinalis* Gaertn., *Terminalia chebula* Retz., *Adhatoda vasica* Nees., *Trichosanthes dioica* Wall., *Fumaria officinalis* L., *Tinospora cordifolia* Miers., Kapardika bhasma, Praval bhasma, and Shauktik bhasma. These components were recognized to have antioxidant along with antiulcer properties and were thus utilized in the innate system of pharmaceuticals to treat gastric ulcers. The safety of the syrup was established by carrying out acute oral toxicity studies as per the OECD guideline 423 and observing the mice for 14 days. The formulation showed neither signs of toxicity nor mortality up to a dose of 5000 mg/Kg. The antiulcer potential of Normacid syrup (250 and 500 mg/kg *p.o.*) was evaluated by the Pylorus ligation model and the Diclofenac-induced ulcer model by comparing with Ranitidine (20 mg/kg *p.o.*) as standard. The parameters assessed include gastric juice volume, pH, total acid, free acid, mucin secretion, ulcer index, and levels of MDA, SOD, CAT, and GSH. Evaluation of the parameters revealed a significant decrease in the volume of gastric juice, free acid, total acid, ulcer index, and MDA levels. In contrast, there was an increase in pH, mucin secretion, and levels of nitrites, SOD, CAT, and GSH. Treatment with Normacid syrup also attenuated the histopathological changes making the gastric mucosa more regular with the absenteeism of ulcerations. Thus, the authors concluded that the cytoprotective outcome of Normacid syrup might be due to its scavenging action on reactive oxygen species or self-protective action by mucosal nitrite and mucin. [26]

### *3.14 Shivaksharpachan Churna*

Shivaksharpachan Churna consists of one part each of the fine powders of *Piper longum* Linn., *Zingiber officinale* Roscoe, *Piper nigrum* Linn., *Ferula foetida*, *Cuminum cyminum* Linn., *Terminalia chebula* Retz., *Trachyspermum ammi* Linn., and Sarji-kshara. A preliminary phytochemical evaluation was carried out to confirm the phytoconstituents. Acute toxicity studies confirmed the safe dose to be 2000 mg/kg. Pylorus ligation and ethanol-induced ulcer models were used to evaluate the antiulcer potential of the formulation (50, 100, and 200 mg/kg *p.o.*) in comparison with Ranitidine (100 mg/kg *p.o.*) as standard. Parameters such as LPO, CAT, and SOD were assessed for the antioxidant activity in the ulcer models. The qualitative phytochemical assessment of the extract disclosed the existence of saponins, flavonoids, bitter principles, steroids, and phenols in the extract. Pre-treatment with the extract was found to significantly reduce lipid peroxidation and rise CAT and SOD levels when related to the control group. The authors concluded that the possible mechanism of the gastroprotective activity could be via antioxidant action of the constituents of the formulation.[27]

### *3.15 Gasteon Syrup*

Gasteon syrup comprises *Asparagus racemosus, Glycyrrhiza glabra, Hedychium spicatum*, Shankha Bhasma, Kapardika Bhasma, and Kamdudha Rasa. *Glycyrrhiza glabra,* and *Asparagus racemosus* are proven for antisecretory and antiulcer actions. *Hedychium spicatum* showed a protective effect against the histamine-induced model of ulcer. Alkaline Shankha Bhasma is known for its antiulcer effect and is indicated for dysentery, loss of appetite, duodenal ulcer, and hyperacidity. Kamadudha Rasa and Kapardika Bhasma is evident of antacid action. Acute oral toxicity was performed by OECD guideline 425, and the animals were observed for 14 days. The No-Observed-Adverse-Effect-Level (NOAEL) of Gasteon syrup was recorded as 2000 mg/kg. Pylorus ligation technique was utilized to induce ulcer lesion with Ranitidine (27 mg/kg) as standard. Syrup at the dose of 25 mg/kg was evaluated for effects on the pH of gastric content, total acidity, gastric volume, free acidity, and ulcer index. Also, the effect on oxidative stress markers SOD, catalase, and LPO-MDA was estimated. A significant rise in pH, SOD, and catalase activity was observed in the test group. Decreased gastric content volume, ulcer index, lipid peroxidation, free, and total acidity were logged. The favorable outcome of stress markers suggested the role of antioxidant action in the mechanism of ulcer healing.[28]

### *3.16 Laghusoothshekhar*

As per Nav Samhita, Laghusoothshekhar comprises three ingredients, *viz*, Piper *betle*, *Suvarna gairik*, and *Zingiber officinale.* The efficacy of *Zingiber officinale* had been noted in gastritis and ulcers. It was also found to possess *in vitro* anti-*H. pylori* activity. *Piper betle* enhanced the adhering mucus content to the gastric mucosal wall. It also inhibited the free radicals involved in the pathology of ulcers. *Suvarna gairik,* an oxide of iron, is efficacious against various vomiting, burning sensations, bleeding disorders, diseases of the abdomen, and emesis. This provided the basis for the confirmation of protective action against ulcerogenic lesions. Shay's pyloric technique was utilized for the induction of ulcers in laboratory animals. Laghusoothshekhar (50 and 100 mg/kg) and Ranitidine (25 mg/kg, standard) were assessed for ulcer index and percent protection as related to control. Statistical analysis of the observations led to the conclusion that animals pre-treated with 100 mg/kg showed actions comparable to Ranitidine. The authors claimed the synergistic action of the components present in the formulation. Moreover, the exclusive technique of preparation, *Bhavana*, plays a crucial role in the augmentation of its activity.[29]

### *3.17 Amukkara Choornam*

Amukkara choornam is a Siddha PHF, marketed by SKM Siddha and Ayurvedic Medicines India (P) Ltd, Erode. It comprises of spices and herbs, used for tuberculosis, spleen enlargement, hiccups, leucorrhea, gastric ulcers, and anemia. The formulation contains fine powder of *Elettaria cardamomum* Maton., *Piper longum* Linn., *Withania somnifera* Dun., *Syzygium aromaticum* Linn., *Zingiber officinale* Rosc., *Cinnamomum wightii* Blume., *Piper nigrum* Linn., and cane sugar. The literature survey uncovered diverse mechanisms exhibited by these components in the defensive impacts against ulcers. Antistressor activity of *Withania somnifera,* urease activity of *Cinnamomum wightii,* inhibition of gastric lesions by *Elettaria cardamomum,* inhibition of acid and pepsin secretory action of *Zingiber officinale,* and incitement of mucus synthesis by *Syzygium aromaticum* had been reported by researchers. Phytochemical screening of the formulation affirmed the existence of phenols, bitter principles, flavonoids, saponins, and steroids. A large content of piperine, eugenol, and trans-caryophyllene was found to be present in the formulation, as uncovered by the HPTLC analysis. These constituents possibly promote free radical scavenging, maintenance of mucus membrane integrity, tissue repair, and anti-*H. pylori* actions.

DPPH scavenging activity was undertaken to establish the antioxidant potential of the formulation. In order to further ascertain the beneficial effects of the formulation in gastric protection, antioxidant activity using ethanol-induced and pylorus ligation methods was adopted. Followed by ulcer induction LPO, catalase, and SOD activities were measured at 50, 100, and 200 mg/kg doses of formulation with Ranitidine (100 mg/kg) as standard. The referred study results proved dose-dependent protective effects against gross damaging outcomes in both models. This supported the holistic use of Amukkara choornam in ulcer treatments.[30]

### *3.18 Ulcerene*

*Bambusa arundinacea, Coriandrum sativum, Elettria cardamomum, Foeniculum vulgare, Rosa damascene, Mineral bezoar triturated* and *Pistacia lentiscus* are the components of PHF Ulcerene. The powder was macerated for three days with 70 % aqueous methanolic solvent at room temperature. The extract thus obtained was screened for detection of various phytochemical classes. The phytochemical tests detected positive for tannins, carbohydrates, proteins, alkaloids, phenols, and saponins. For induction of ulcers, ethanol-induced, Aspirin-induced, and stress-induced methods were employed. Test groups received 50 and 100 mg/kg of Ulcerene extracts compared with Sucralfate (100 mg/kg), Misoprostol (100 mg/kg), and Ranitidine (50 mg/kg) as standards for the three models, respectively. Histopathological assessment displayed hyperplasia, focal erosion, infiltration of inflammatory cells, congestion in lamina propria, and chronic superficial gastritis in the control group. Mild or no alterations in the gastric mucosa of animals treated with standard drugs were observed. As compared with the lower dose (50 mg/kg) of Ulcerene, the higher dose (100 mg/kg) showed only mild gastritis, infiltration, and congestion. It was observed that Ulcerene presented a dose-dependent decline in the ulcer score and index. Comparison between different models signified the PHF to be most effective in controlling ethanol-induced lesions.[31]

**Table 1. Polyherbal formulations along with the pharmacological models for antiulcer activity.**

| Sr. No. | Formulation | Composition | Model | Key findings | Reference |
|---|---|---|---|---|---|
| 1. | Yelathy Chooranam | *Taxus buccata, Piper nigrum, Eletaria cardamomum, Syzygium aromaticum, Cinnamomum zeylanicum, Zingiber officinale,* and *Curcuma angustifolia* (Arrowroot) | Aspirin and ethanol-induced acute ulcers in rat models, Cysteamine-induced duodenal ulcers in rat models, and Indomethacin-induced ulcers in rat models | The components significantly showed the cytoprotective effect | 14 |
| 2. | NR-ANX-C Natural Remedies Pvt. Ltd., Bangalore, India | *Camellia sinensis, Withania somnifera, Ocimum sanctum,* shilajit, and Triphala | Aspirin-induced ulcers in the rat model, Pyloric ligature-induced ulcers in rat model | The antisecretory, cytoprotective and antioxidant actions contributed to the antiulcer action | 15 |
| 3. | Livina Dey's Medical Stores (Mfg.) Ltd. | *Solanum nigrum, Holarrhena antidysenterica, Tephrosia purpurea, Andrographis paniculata, Phyllanthus niruri, Tinospora cordifolia, Terminalia chebula, Asteracantha longifolia, Alstonia scholaris, Berberis aristata, Cichorium intybus,* and *Picrorhiza kurroa* | Ethanol-induced ulcers in mice model | Mild lesions were exhibited with a significant reduction in ulcer index | 16 |
| 4. | RO12 Rumi Herbal Research Institute Private Limited, Chennai | *Rosa damascena, Glycyrrhiza glabra, Aegles marmelos, Eletteria cardomum, Citrus aurantifolia,* and *Saccharum officinarium* | Pyloric ligation-induced ulcers in the rat model and Ethanol-induced ulcers the in the rat model | Antisecretory, antioxidant, and cytoprotective actions, along with an increase in the bicarbonate and blood circulation, resulted in the gastroprotective action | 17 |
| 5. | Avipattikar churna | *Terminalia bellerica, Zingiber officinale, Vida Lavana, Piper nigrum, Emblica officinalis, Amomum subulatum, Piper longum, Terminalia chebula, Operculina terpethum, Cyperus rotundus, Embelia ribes, Syzgium aromaticum, Cinnamomum tamala,* and Sharkara | Shay's pyloric technique in the rat model | 500 mg/kg showed significant antisecretory and gastroprotective effects; however, the results were not statistically significant in comparison with Ranitidine | 18 |

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| 6. | VRC/AS/014 syrup Vasu Research Centre, Vadodara | *Emblica officinalis, Asparagus racemosus, Glycyrrhiza glabra, Hemidesmus indicus, Centella asiatica, Terminalia chebula, Terminalia belerica, Ipomoea turpethum, Sodii carbonas,* and Black salt | Aspirin plus pylorus ligation induced ulcer in the rat model | Significant antiulcer and antisecretory properties comparable to Sucralfate established the preclinical scientific data to support the basis for the clinical use | 19 |
| 7. | Digitrall M/s. S. C. Pharmaceuticals Ltd., Kolkata | *Amomum sabulatum, Foenieulum vulgar, Zingiber officinale, Piper nigram, Berberis aristata, Ptychotis ajowan,* and *Carica papaya* | Indomethacin-induced gastric mucosal damage in the rat model | Antioxidant activity was accountable for the antiulcer action | 20 |
| 8. | Pepgard syrup Vital Care Pvt. Ltd., Vadodara | *Glycyrrhiza Glabra, Asparagus racemosus, Astoneman indicum, Emblica officinale, Centella asiatica, Ipomoea turpethum, Syzygium aromaticum, Fumaria officinalis,* and *Coriandrum sativum* | Aspirin-induced ulcers in the rat model | The presence of phytobiological constituents was responsible for the antioxidant and antiulcer action | 21 |
| 9. | Amlapitta Mishran suspension Shree Dhootapapeshwar Limited, Mumbai | *Adhatoda vasica, Tinospora cordifolia, Azadirachta indica, Swertia chirata, Eclipta alba, Trichosanthes dioica, Glycyrrhiza glabra, Phyllanthus emblica, Terminalia chebula, Terminalia belerica, Shouktik bhasma,* and *Fumaria indica* | Indomethacin-induced ulcer in the rat model | Reduction in ulcer index and percent inhibition was a consequence of enhanced prostaglandin synthesis | 22 |
| 10. | Hingwashtak churna | *Piper nigrum, Nigella sativa, Ferula foetida, Zingiber officinale, Cuminum cyminum, Piper longum, Trachyspermum ammi,* and Saindhava lavana | Ibuprofen and Ethanol-induced ulcers in the rat models | The gastroprotective property was attributed to the antioxidant ingredients and increased prostaglandin level | 23 |
| 11. | Qarahine Hamdard laboratories, Pakistan | *Glycyrrhiza glabra* Linn., *Cochlospermum gossypium* DC., *Lapis lazuli, Koalinum ponderosum*, *Pistacia terebinthus* Linn., silicate of magnesia, magnesium silicate, and ferrum | Aspirin and Ethanol-induced ulcer in rat models | Significant reduction in the number of lesions, the severity of the injury, and ulcer index was seen, indicating the antiulcer activity | 24 |
| 12. | Phy-Blica-D | *Glycyrrhiza glabra, Aegle marmelos, Phyllanthus emblica, Terminalia arjuna, Terminalia bellirica, Cyperus rotundus, Maerua siamensis, Terminalia citrina, Piper retrofractum, Zingiber officinale, Alpinia galanga, Solanum torvum, Allium sativum,* and *Tinospora crispa* | Ethanol-induced acute gastric lesions in the rat model | The possible mechanism of the gastroprotective effect could be the free radical scavenging action | 25 |
| 13. | Normacid syrup Ayurlab herbals Pvt. Ltd., Vadodara | *Ficus glomerata* Roxb., *Fagonia Arabica* L., *Vetiveria zizanioides* Stapf., *Santalum album* L., *Andrographis paniculata* Nees., *Melia azadirachta* L., *Terminalia bellerica* Roxb., *Emblica officinalis* Gaertn., *Terminalia chebula* Retz., *Adhatoda vasica* Nees., *Trichosanthes dioica* Wall., *Fumaria officinalis* L., *Tinospora cordifolia* Miers., Kapardika bhasma, Praval bhasma, and Shauktik bhasma | Pylorus ligation and Diclofenac-induced ulcer in the mice models | Scavenging of reactive oxygen species and enhancement in mucosal nitrite and mucin could be responsible for the absenteeism of ulcerations in the gastric mucosa | 26 |
| 14. | Shivaksharpachan Churna | *Piper longum* Linn., *Zingiber officinale* Roscoe, *Piper nigrum* Linn., *Ferula foetida*, *Cuminum cyminum* Linn., *Terminalia* | Pylorus ligation and Ethanol-induced ulcers in the rat models | The significant antioxidant activity could be the possible mechanism of the | 27 |

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| | | *chebula* Retz., *Trachyspermum ammi* Linn., and Sarji-kshara | | gastroprotective activity | |
| 15. | Gasteon syrup | *Asparagus racemosus, Glycyrrhiza glabra, Hedychium spicatum*, Shankha Bhasma, Kapardika Bhasma, and Kamdudha Rasa | Pylorus ligation technique in the rat model | The role of antioxidant action in the mechanism of ulcer healing was due to the favorable outcome of stress markers | 28 |
| 16. | Laghusoothshekhar | *Piper betle*, *Suvarna gairik*, and *Zingiber officinale* | Shay pyloric technique in the rat model | The components of the formulation showed synergistic action. The augmentation of the activity was attributed to *Bhavana*, the exclusive technique of preparation | 29 |
| 17. | Amukkara choornam SKM Siddha and Ayurvedic Medicines India (P) Ltd, Erode | *Elettaria cardamomum* Maton., *Piper longum* Linn., *Withania somnifera* Dun., *Syzygium aromaticum* Linn., *Zingiber officinale* Rosc., *Cinnamomum wightii* Blume., *Piper nigrum* Linn., and cane sugar | Ethanol-induced and pylorus ligation methods in rat models | A dose-dependent protective effect was proved to support the holistic use in ulcer treatments | 30 |
| 18. | Ulcerene | *Bambusa arundinacea, Coriandrum sativum, Elettria cardamomum, Foeniculum vulgare, Rosa damascene, Mineral bezoar triturated* and *Pistacia lentiscus* | Ethanol-induced, Aspirin-induced, and stress-induced methods in rat models | A dose-dependent decrease in the ulceration was seen with the most significant action in ethanol-induced lesions | 31 |

***Table 1 illustrates a brief review of the antiulcer potentials of some marketed polyherbal formulations. Enlisted herein are the proprietary names and compositions of the PHF. Various preclinical animal models used for the assessment of the antiulcer activities and the key findings are enlisted along with the references for the respective formulations.***

## 4. CONCLUSION

Peptic ulcer is a pathology of concern due to its increasing prevalence worldwide. The current allopathic regimen being utilized in the treatment of ulcers tend to result in side effects that are often distressing and inconvenient. Hence, the search for more suitable alternate medications continued to lead to the development of herbal preparations against ulcers. In recent years, the advantages of polyherbal formulations have been identified, such as synergism, convenience, high efficacy, wider therapeutic window, and cost-effectiveness. With this, an advent in the use of PHFs in the treatment of ulcers has augmented. The PHFs discussed in this review possess significant antiulcer potential and thus provide the scientific basis for their societal use. However, the abundant scope is available for more extensive pharmacological and clinical studies on these PHFs.

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## 6. AUTHOR'S CONTRIBUTION STATEMENT

The work was conceptualized by Dr. Manish Kumar Gupta. Mrs. Medha Amol Khade and Dr. Amol Baban Khade collected and edited the data. The first draft was prepared by Mrs. Medha Amol Khade. Dr. Birendra Shrivastava and Dr. Supriya Rajesh Hyam critically evaluated the manuscript and gave their valuable inputs. All the authors examined the ultimate version and affirmed it for publication.

## 7. CONFLICT OF INTERESTS

Conflict of interest declared none.

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